Editorial

It is now almost 5 years since we started the journal *Green Chemistry* and time to pass on the baton to a new Scientific Editor to help lead the great race towards a sustainable future through green chemistry.

I shall always remember the excitement and anticipation when, after many meetings and much soul searching, we planned the first issue in 1998. The growth in the journal submissions and subscriptions, the increase in quality of its contents and the widespread acceptability of the journal as a leading scientific publication, make the great efforts of the original planning group, the RSC staff, my colleagues at York and the people who have sat on the editorial boards seem very worthwhile.

What have been the major developments in green chemistry since we started? One of the most encouraging developments must be the internationalisation of the movement. There has been a steady growth in the number of national and international conferences on green chemistry and those interested can now pick and choose from numerous meetings each year including more specialist areas such as alternative solvents and intensive processing. Green chemistry networks have been set up in recent years in countries including Japan, Australia, Spain and Canada. In the last few weeks I have heard of new networks being established in Greece and Portugal. These networking activities will help to better co-ordinate the growing interest in green chemistry within countries and hopefully in the future, we will see more collaboration between these organisations.

We have also seen an increasing recognition of the importance of a multi-disciplinary approach to green chemistry. Those of us in the chemistry community have often referred to chemistry as a central science but this means that we have to look at other disciplines for links and collaboration. Progress towards achieving the principles of green chemistry needs chemists, engineers, environmental scientists and others to work together and it has been pleasing to see a significant number of publications in *Green Chemistry* from outside the main chemistry community. I look forward to seeing these links grow and flourish and for new links to be established, for example, with specialists in economics and social policy. Green chemistry means achieving the 'triple bottom line' of economic, environmental and social benefit.

The last five years have also seen some good examples of green chemistry put into industrial manufacture. These cover the supply chain with greener products (*e.g.* new surface coatings and chelating agents), greener processes (*e.g.* through the use of supercritical carbon dioxide in fine chemical manufacturing) and the use of renewable feedstocks (*e.g.* new biodegradable materials derived from plants). It was pleasing to see that Greenpeace have highlighted such examples of green chemistry in practice in their recent document "Safer Chemicals within Reach. Using the Substitution Principle to drive Green Chemistry". It is through real commercial examples of the triple bottom line at work that we can expect to see increased exploitation of green chemistry in the future.

The importance of green chemistry in education is paramount. Chemists and technologists of the future should automatically consider the principles of green chemistry when they are working in industry and research. In this journal we have seen some good examples of new green chemistry teaching materials. Through green chemistry we have a unique opportunity to again make chemistry an exciting and relevant subject for future generations and to put chemistry in the centre of the movement towards creating a sustainable society. We must continue to find innovative and exciting ways to influence the educational process at all levels. The great race towards a sustainable future is a marathon not a 'sprint'!

I am delighted that Walter Leitner and his team have agreed to take over the scientific editorship of *Green Chemistry*. My colleagues Helen Coombs and Duncan Macquarrie join me in wishing them every success in the future and we look forward to seeing *Green Chemistry* continue to flourish.

James Clark, York, November 2003

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New Scientific and News Editors from 2004

Scientific Editor

Walter Leitner was born in Pfarrkirchen, Bavaria, on 2 February 1963. He is married to Andrea Leitner and they have two children (Eva-Maria, 10, and Johannes, 8). He is Professor for Technical Chemistry and Petrochemistry at the RWTH Aachen (successor to Willi Keim) and External Scientific Member of the Max-Planck-Institute for Coal Research, Mülheim, Germany. His research interests are focused on transition metal complexes as catalysts for chemical transformations and the use of supercritical fluids as benign reaction media. The scientific achievements of his group have been recognized *inter alia* with the Gerhard-Hess-Award of the German Science Foundation, the Carl-Zerbe-Award, the 2nd International Messer Innovation Award and the Otto-Roelen-Medal. He is co-editor (with P. G. Jessop) of the book "Chemical Synthesis using Supercritical Fluids" and chairman of the conference series "Green Solvents for Synthesis".

News Editor

Markus Hölscher received his Ph.D. from the RWTH-Aachen for the synthesis and characterization of microporous heteropolytungstates and –molybdates with Professor W. Hölderich in 1995. From 1995 he worked as editor and interpreter for *Angewandte Chemie*, but in 2000 he joined Professor Höcker's group, investigating the mechanisms of zirconocene-catalyzed polymerisations of acrylates by means of quantum chemical calculations. In 2002 he moved to Professor Leitner's group, exploring the mechanisms of transition metal-catalyzed reactions using theoretical calculations.

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Barry M. Trost

A profile of Barry Trost, outlining his career and contribution to green chemistry

Barry M. Trost was born in Philadelphia, Pennsylvania, USA on June 13, 1941. As this was the adopted home of Benjamin Franklin, he was exposed to science at an early age and was strongly attracted by the excitement of discovery that it offered. Coming from a middle class immigrant family, he was the first of his family to go to a university. He went through the Philadelphia public schools and was awarded a full tuition scholarship to attend the University of Pennsylvania, graduating *cum Laude* in 1962. The beauty and intellectual challenges of organic chemistry exemplified by the extraordinary teaching of Allan Day and Madeline Jouillié there revealed this field as his calling. During this time, he performed independent study in the laboratory of a new Assistant Professor, Edward Thornton. Thornton, coming from MIT, persuaded him to pursue his graduate studies at MIT which he completed in less than three years. The topic of his dissertation under the direction of Herbert O. House was the structure and reactivity of enolates.

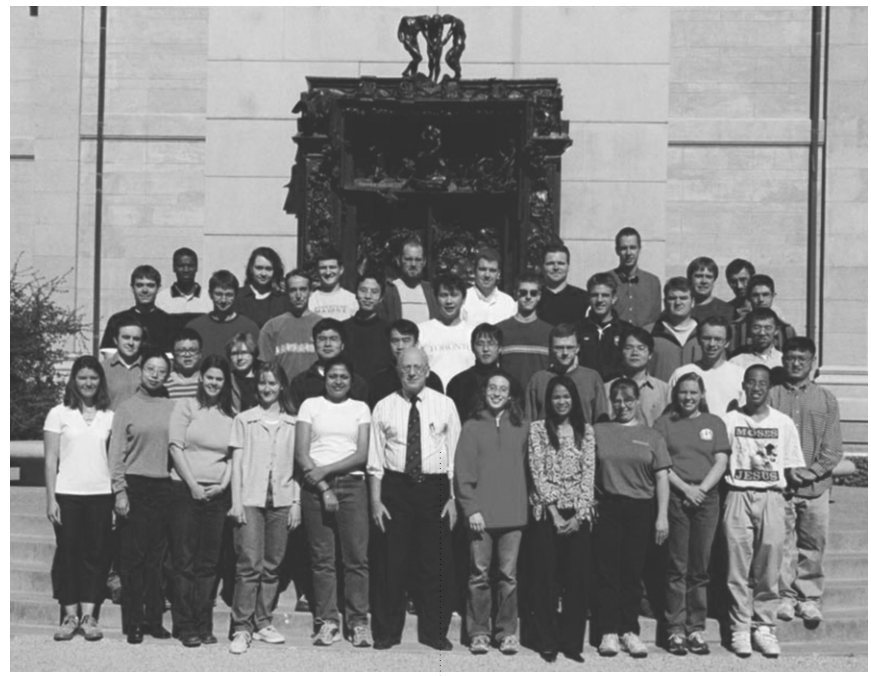
Upon graduating from MIT in 1965, he joined the University of Wisconsin-Madison as an Assistant Professor and was rapidly promoted to Associate Professor (in 1968) and Professor (in 1969). He was appointed to an endowed chair, the Helfaer Professor in 1976, and in 1982 to one of the most prestigious endowed chairs at the University, the Vilas Research Professorship. From 1980–1982, he served as Chair of the department.

In Madison, he met Susan Paula Shapiro who became his lovely wife in 1967. Their sons, Aaron David and Carey Daniel, were born in Madison in 1970 and 1973. Madison, a relatively small town dominated by being the site of the major campus of the University of Wisconsin and state government, was home for over twenty years and a wonderful place to raise a family. It was a difficult and highly emotional decision to leave this bucolic spot to accept a position at Stanford University in 1987. In 1990, he was appointed to the newly created endowed chair, the Job and Gertrude Tamaki Professorship in the School of Humanities and Sciences. Upon arriving in California, the family settled in the small town of Los Altos Hills, a bedroom community adjoining Palo Alto, the site of Stanford University. Being in the heart of Silicon Valley makes the area a truly exciting and dynamic one of at the cutting edge of science and technology.

During his career, he has held several Visiting Professorships in Europe including Germany—University of

Marburg (1972), the University of Hamburg (1985) and the University of Munich (1988), France—Université Pierre at Marie Curie, Paris VI (1986), University of Paris–Orsay (1990), Italy—University of Pisa (1992), Denmark—University of Copenhagen (1979), Spain—University of Barcelona (1987), University of Santiago de Compostela (2002), and the United Kingdom—University of Cambridge (2002). He was awarded a Docteur *honoris causa* from University of Lyons (1994) and Doctor Scientiarum Honoris Causa from the Technion, Israel in 1997.

His research program from the beginning focused on organic synthesis. Upon initiating his independent career, he took up the theme of designing and



†Photographs show Professor Trost receiving his Presidential Green Chemistry Award from the EPA administrator, with his research group and with his wife attending a conference in Japan.

DOI: 10.1039/b312272g

synthesizing organic conductors which led to the first synthesis of pyracylene—a molecule whose carbon framework was discovered about 20 years later as a feature of the fullerenes. At the same time, he collaborated with Herbert Röller and Karl Dahm on the structure determination and synthesis of the insect juvenile hormone. The latter had a profound impact upon his future efforts. A major theme revolved upon organosulfur chemistry. The study of the chemistry of sulfur ylides led to the development of the cyclopropylides as particularly useful reagents. The development of the concept of the sulfenylation of anions led to many novel transformations, one of the most notable being the subsequent thermolysis of the related sulfoxide as a chemoselective route to introduce double bonds. The discovery of the ability of sulfones to function as leaving groups led to the concept of their functioning as 'chemical chameleons' because of their ability to serve as both nucleophiles and electrophiles for carbon–carbon bond formations simply depending upon reaction conditions.

However, it was thinking about synthetic routes to the juvenile hormone that led to the development of the field of allylic alkylations and catalysis in general which became the overriding theme of his research program. It also stimulated his thinking about the nature of the challenges of synthesis. What were the issues that needed to be resolved as one looked toward inventing new reactions? He formalized his thinking around the themes of selectivity. First and foremost, reactions must be capable of differentiating among various bond types—not only between two different kinds of bonds such as C=O and C=C but, more importantly, between two similar bonds such as two different C=O present in the same molecule—a type of selectivity he termed chemoselectivity. Second is regioselectivity or controlling the orientation in which two reacting partners approach one another. The third area deals with controlling stereochemistry either in a relative fashion (or diastereoselectivity) or absolute fashion (enantioselectivity). From an academic point of view, the challenges of synthesis ended with the issues of selectivity. However, from a practical point of view, a major issue of immense importance was being ignored and even sacrificed in order to solve problems of selectivity. The issue relates to the question of how much of what is put in a pot ends up as product or waste. Clearly, to optimize the use of raw materials and concurrently minimize the generation of waste, we want to strive to use 100% of the starting materials to form the product with anything else only needed catalytically which, for want of a better term, he referred to as atom economy. Thus, the theme of his program became to enhance synthetic efficiency by addressing the twin goals of selectivity and atom economy.

Two strategies are pursued—improving existing reactions or inventing new paradigms—wherein catalysis is an overarching theme. The first endeavor—developing the concept of alkylation α to a carbon–carbon double bond (*i.e.* allylic alkylation) as an adjunct to the common alkylations α to a carbonyl group—led to the study of the organic chemistry of palladium, molybdenum and tungsten. These efforts indeed led to addressing all the issues of selectivity and, in many cases, also addressed the problem of atom economy by developing new simple addition reactions such as the additions of pronucleophiles to allenes or vinyl epoxides. In some cases, the rules of selectivity totally change such as net S_N2 substitution with retention of configuration rather than inversion. Placing emphasis on atom economy led to the study of the organic chemistry of ruthenium, rhodium, and vanadium. The study of ruthenium catalyzed reactions alone led to the invention of 26 new processes to date using only one type of complexes as catalysts. Improving existing reactions has addressed the classical aldol reaction during which a novel class of ligands led to the spontaneous assembly of dinuclear metal complexes as a new class of catalysts. All of this is performed in conjunction with efforts of total synthesis of complex biologically active molecules with the goal of revealing heretofore unknown synthetic strategies.

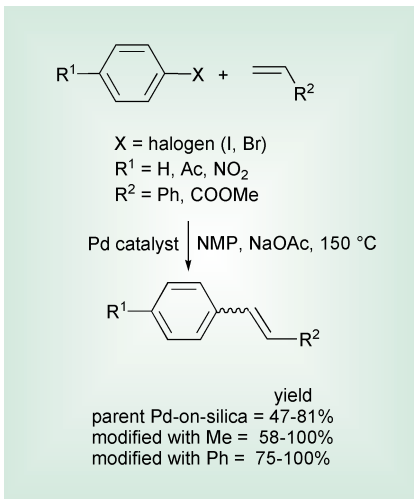
The central nature of synthesis cannot be overstated. It is the enabling science that permits addressing problems ranging from material science to medicine. Removing constraints upon design of structure for function is critical for the future. To the extent that structural design is greatly restricted by accessibility, the ability to address problems is tremendously limited. Sometimes the power of existing methods leads some to conclude that we have all the methods we need. Such a myopic view cannot be further from the truth. What potentially can be possible is hard to imagine. However, one conclusion can be made with a high degree of certainty—we have only uncovered an infinitesimally small part of reaction space. It has been estimated that, to date, we have only synthesized $1/10^{38}$ of the total of compounds of molecular weight ≤500 daltons containing only C, H, N, O, P, S, F, Cl and Br. It is obvious that we will have synthesized an even smaller number if we include elements across the entire periodic table. Since performing reactions typically involves reacting two or more substances, the number of permutations grow even more astronomically. Clearly, we have barely begun to discover what is possible.

Highlights

Duncan Macquarrie reviews some of the recent literature

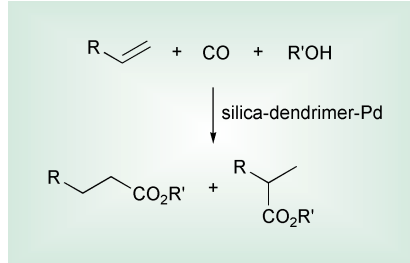
Pd catalysis

The subject of heterogeneous Pd catalysts for C–C bond forming reactions is being studied intensively. A recent communication for the group led by Árpád Molnár at the University of Szeged is interesting in this area (*Chem. Commun.*, 2003, 2626). They have modified silica with $Cl_nR_{32n}SiH$ to give (organically modified) silica with Si–H bonds. These bonds cause the reduction of



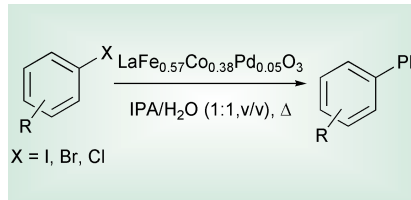
adsorbed Pd species to generate Pd metal on the surface. They found that the catalysts formed were very good catalysts for the Heck reaction, and that activity depended both on Pd content and the presence of a single organic group at the Si–H unit (preferably Ph). They also found that there was some loss of Pd into solution during reaction, the soluble Pd being of low activity, and that virtually all of the Pd returned to the solid after reaction.

Hydroesterification reactions are one of the lesser studied Pd catalysed reactions, but are nevertheless of great relevance. Jan Reynhardt and Howard Alper of the University of Ottawa have developed a heterogeneous catalyst for this purpose (*J. Org. Chem.*, 2003, **68**, 8353). Their catalyst is based on supported dendrimeric phosphines. These catalysts have been extensively characterised and evaluated for the reaction of alkenes, CO and alcohols, and very good results have been obtained, with very high conversions



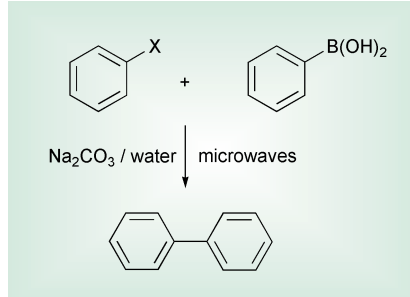
and very good reusability of the catalyst. Of equal importance, the linear product is, unusually, favoured in all cases.

Steven Ley and his group at Cambridge University have published results on a perovskite-supported Pd system (*Chem Commun.*, 2003, 2652). Their choice of support comes from observations in other areas which suggest that the material can "self-regenerate" with the possibility of



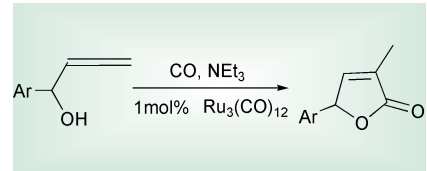
longer catalyst lifetimes. The Pd–perovskite system was efficient for the coupling of a range of aryl halides with boronic acids under standard conditions. Microwave heating allowed the ready conversion of the more difficult aryl chlorides too. As in the previous system, there is evidence of a release–catalysis–recapture mechanism.

Chao-Jun Li of McGill University in Montreal has published a very interesting highlights paper on Pd-free Suzuki reactions (*Angew. Chem., Int. Ed.*, 2003,



42, 4856). This paper discusses recent results from Leadbeater which indicate that the Suzuki reaction can be carried out in water without metal catalysis. Microwave heating is required. Li speculates on possible mechanisms which do not require the metal-induced bond cleavage and formation central to the "traditional" Pd-catalysed route.

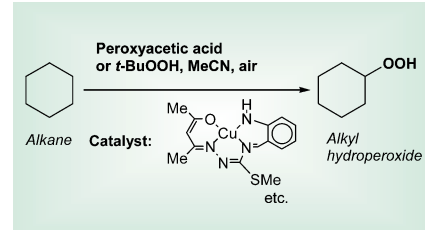
Ruthenium carbonyl has been used by Shigetoshi Takahashi and his group from Osaka University in an impressive synthesis of lactones and lactams (*J. Org. Chem.*, 2003 **68**, 8571). They used catalytic quantities of the trinuclear



complex along with CO and triethylamine to convert allenyl alcohols directly to lactones in excellent yields and with 100% atom economy. Using allenyl amines in place of the alcohols led to lactams. Both 5 and 6-membered rings can be formed in essentially quantitative yields using this method.

Oxidation reactions

The oxygenation of cyclohexane (and other alkanes) is an important step in the valorisation of these compounds. Georgiy Shul'pin and co-workers from the Semenov Institute of Chemical Physics in Moscow have provided details of Cu catalysed oxidations of cyclohexane (*Org. Biomol. Chem.*, 2003, **1**, 3611). They show that, with peracetic acid as oxidant, good conversions of cyclohexane (to the peroxide, alcohol and ketone) can be



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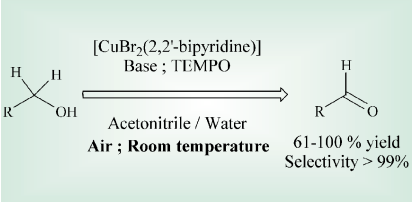
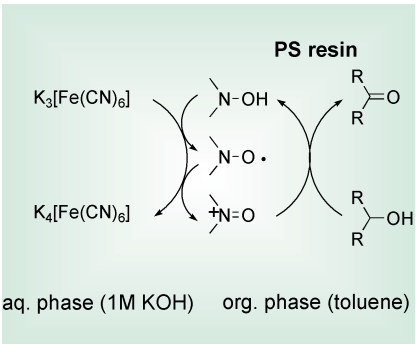
achieved, even with simple Cu salts such as the acetate. Complexes are also useful oxidants, although the choice of ligand is crucial, with wide fluctuations in the performance being noted with only minor changes in ligand design.

The selective transformation of alcohols to aldehydes is an important and difficult process. Roger Sheldon's group at the Technical University of Delft have developed a simple and effective method for doing this (*Chem. Commun.*, 2003, 2414). The combination of copper(II) bromide, bipyridyl, TEMPO and base (all



in catalytic quantities) allows the highly selective and high yielding synthesis of a number of aldehydes using air as the terminal oxidant. The process takes a few hours at room temperature, making it a very mild process. Copper perchlorate was slightly better than the bromide, with other anions being less good; this effect was assigned to the degree of coordination of the anion, the lower the better.

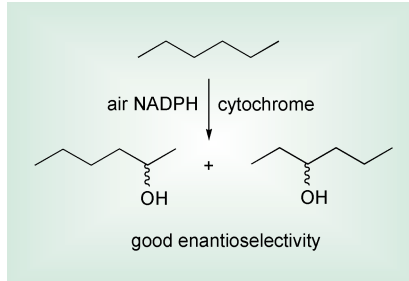
A further TEMPO-mediated oxidation is worth mentioning, although it is not terribly green as it stands. Yoshitomo Kashiwagi and his colleagues at Tohoku University in Sendai have developed a TEMPO catalysed oxidation of alcohols



to aldehydes using potassium hexacyanoferrate as oxidant (*New. J Chem.*, 2003, **27**, 1545). The results they obtain are very promising and hint at a distinct chemoselectivity which should allow the oxidation of primary alcohols in the presence of secondary OH groups.

While the system as it stands uses stoichiometric quantities of the oxidant, the low redox potential ($E\Delta$ = 0.36 V) suggests that it might be relatively simple to re-oxidise this *in situ*, and make the process catalytic.

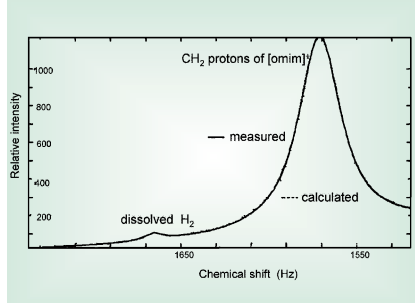
The direct formation of chiral alcohols from alkanes and oxygen seems a remarkably optimistic goal. However, Frances Arnold and colleagues at the California Institute of Technology have achieved just that (*J. Am. Chem. Soc.*, 2003, **125**, 13442). They engineered cytochrome P450 BM-3 to give a very



active and efficient biocatalyst, which, in conjunction with NADPH and air gave (*S*)-3-nonanol from nonane in 83% ee. Other nonanols were also formed at the same time, indicating that regiocontrol is not perfect, with 2- and 3-alcohols being preferred. Several other alcohols could be oxidised, generally with ee's <50%, but with some above 60%. Traces of ketones were formed in some cases.

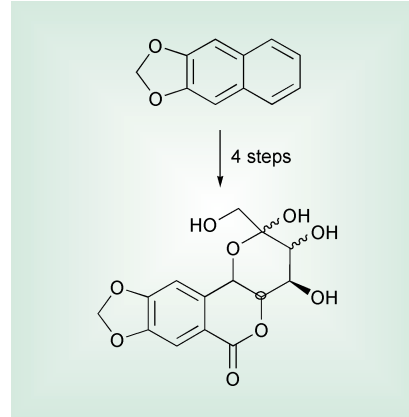
Ionic liquids

The solubility of hydrogen in ionic liquids is an important parameter which contributes to the knowledge base of these solvents. Paul Dyson and his group at the Ecole Polytechnique Fédérale of Lausanne have measured this solubility by high pressure NMR techniques (*Chem. Commun.*, 2003, 2418). They found that the solubility was very low, much lower than that of most organic solvents. However, they found no correlation between solubility and rate of hydrogenation, suggesting that the solubility of hydrogen in the substrate was helping to minimise differences seen in the pure ionic liquids.



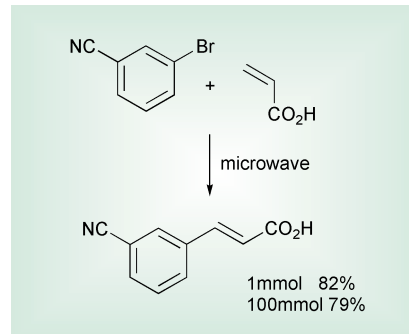
Biocatalysis

Pancratistatin is a molecule which is attracting considerable interest for its biological properties. Analogues of this molecule are important to define the minimum structural requirements for biological activity, but its structure poses significant synthetic challenges. Wolf-Dieter Fesser and colleagues from the



Technical University of Darmstadt have now published an elegant and simple 4-step biocatalytic route to these molecules (*Angew. Chem., Int Ed.*, 2003, **42**, 4821). Their route gives a modest yield, but is direct and operates under mild conditions. No protection/deprotection stages are required.

Microwave activation is receiving significant attention at present, and many interesting results are being obtained. Oliver Kappe and his co-workers at Karl-Franzens University in Graz have now published data which indicate that this technique can be scaled up with little effect on efficiency (*Org. Proc. Res. Dev.*, 2003, **7**, 707). A variety of reaction types



were investigated, and it was found that all of them could be scaled from 1 mmol to 100 mmol scale with little difficulty. Heating rates were very similar on both scales. However, cooling was not as efficient, taking several times longer on a large scale. This did not cause any significant changes in the outcome of the reactions.

The first Worldwide Universities Network symposium on green chemistry

Louise Summerton at the University of York describes the first Worldwide Universities Network Symposium on Green Chemistry.

The Worldwide Universities Network (WUN)† is an international alliance of leading universities who are working together to take advantage of research and educational opportunities emerging in rapidly moving interdisciplinary areas of global significance, one of which is green chemistry. The 1st International Worldwide Universities Network Meeting entitled "Excellence in Green Chemistry" was held in San Francisco on 10th October 2003. This one day research symposium was organised by the WUN Green Chemistry Working Party in co-operation with the Green Chemistry Network (GCN), based at the University of York.

†Further information about the WUN can be found at www.wun.ac.uk or by contacting Louise Summerton at ls25@york.ac.uk

Representatives from seven of the thirteen WUN partner institutions (Illinois, Penn State and Washington State in the USA, Leeds, Manchester, Southampton and York in the UK) attended the symposium. Fascinating presentations were given on a wide array of topics, ranging from the development of cleaner synthetic routes through to new analytical methods, engineering issues and resource recovery. The oral presentation topics were Selective Oxidation Catalysts for Green Chemical Synthesis, Green Colour Chemistry, Analytical Resources for Green Chemistry, Spectroscopy of the Interface in Liquid–Liquid extraction, Overview of Renewables for Chemicals and Fuels, Engineering Better Products, Environmental Remediation of Soil and Groundwater, A Leeds Perspective, Enhancing *in situ* Bioremediation in light of Ecological Considerations, Facilitated Synthesis *via* Polymer-supported Reagents, Catalysts and Scavengers, Turning Food Processing Waste into Electricity using a fast two-phased Fermentation System, Chemicals and Chemical Feedstocks from Renewable Raw Materials and Green Chemistry at Illinois.

Overall, the symposium was very well received and will hopefully be the first of many WUN Green Chemistry symposia. The quality of the research presented truly demonstrated 'Excellence in Green Chemistry' and proved that green chemistry is unquestionably at the cutting edge of scientific advancement. This invaluable opportunity for the partner institutions to share information and discuss their ideas will hopefully lead to the development of further successful and effective research collaborations.

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The first conference on Green Chemistry in Poland: EkoChemTech'03

Romuald Bogoczek, Chairman of the conference, describes this important new event

The Conference was held in Wroclaw on June 27–28 2003 at the University of Economics.

There were about 70 participants, mostly from Poland, but 10 of them came from abroad, *i.e.* from Germany, Switzerland, Romania and Ukraine. The official language was Polish, but the foreign lectures were held in English. The President of the Wrocław University of Economics, Professor Marian Noga, a member of the upper Chamber of the Parliament of the Polish Republic, was the Protector of the Conference. The scientific Committee consisted of Professors, Polish pioneers in green chemistry, coming from all over the country. They were: Romuald Bogoczek (the Chairman of the conference), from *Akademia Ekonomiczna* in Wrocław, Bogdan Burczyk, from *Politechnika Wrocławska*, Tadeusz Paryjczak, *Politechnika Łódzka*, Juliusz Pernak, *Politechnika Poźnanska*, Bolesław Skowroński, *Instytut Nawozów Sztucznych Puławy*, Marian Taniewski, *Politechnika Śląska* and Józef J. Ziółkowski, *Uniwersytet Wrocławski*.

According to the plan/submission, the conference focused on:

1. The essence of 'green chemistry' (green and sustainable industrial chemistry—chemical technology)—12 submissions
2. Reproducible raw materials for 'clean' chemistry—6 submissions
3. New green chemicals and materials—10 submissions
4. Multiphase catalysis—a chance for green chemistry—5 submissions
5. Green solvents used in chemical processes (ionic liquids, supercritical carbon dioxide, organic solvents in the supercritical state, organic solvents in near-supercritical state)—5 submissions
6. Processes with a diminished load to the environment—4 submissions
7. Processes with a diminished energy requirement—0 submissions
8. The utilisation of microwave heating in technological processes and/or technological operations—7 submissions
9. Modern utilisation processes—9 submissions

It is worth stating that there were no submissions for point 7, whereas 9 papers were submitted on a topic not originally proposed by the organisers: modern utilisation processes.

All in all there were 58 papers submitted for presentation: 14 as plenary lectures, 16 as lectures and 28 as posters.

The conference was opened by the Chairman Professor R. Bogoczek followed by the Patron of the conference, Professor M. Noga. Then, after a short break, the lectures began. The titles of all the lectures as well as the posters can be found on the Internet at http://zielonachemia.ae.wroc.pl/harmon_eng.htm

Snapshots of the conference are presented at http://zielonachemia.ae.wroc.pl/fotki/fotki.htm

The first Green Chemistry conference in Poland showed the scientific centres where green chemistry investigation is performed, as well as the main topics of interest in Poland. A large green chemistry didactic activity is evident, as well as a significant theoretical approach to the movement. Industrial achievements include a supercritical extraction of plant species by CO_2. The conference resulted in a 109 page Book of Abstracts (Polish) and numerous papers will be published in English. It was said that the Conference was a remarkable scientific and social success and that it should be continued regularly, say, every two years.

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"Green" oxidation reactions—application to carbohydrate chemistry

Communication

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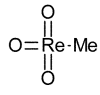
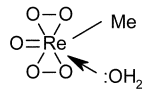
Oxidation of glycals by either methyltrioxorhenium (MTO)–hydrogen peroxide or hydrogen peroxide–acetonitrile in methanol provides direct access to methyl glycosides. The two different reagents proceed with a complementary stereochemical outcome enabling the synthesis of β-D-*gluco*-pyranosides or α-D-*manno*-pyranosides from the same carbohydrate precursor.

Introduction

The development of oxidation processes which are environmentally friendly is currently the focus of much attention.[1] The use of hydrogen peroxide[2,3] in this context is particularly appealing as the inorganic by-product, water, is benign and presents a number of practical advantages (*e.g.* product separation) which may be important especially in an industrial context. The oxidising system comprising of catalytic methyltrioxorhenium (MTO)[4] as the oxygen carrier in conjunction with hydrogen peroxide as re-oxidant is currently one of the most promising in this context. These oxidation reactions, which are thought to proceed *via* the *in situ* generation of the peroxo species **1**, are relatively robust, show good catalytic turnover and are effective in a number of transformations.[5]



MTO

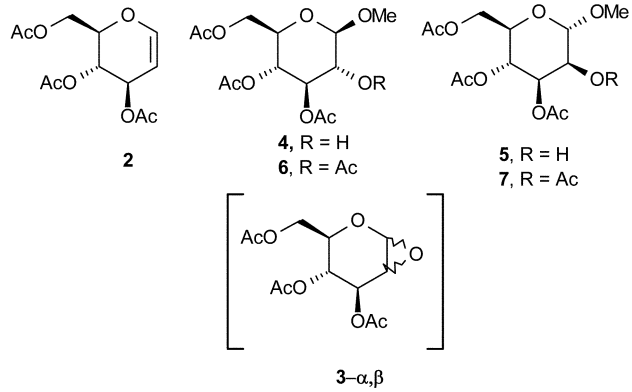


1

Results and Discussion

In the course of a synthetic project we wished to convert glycal derivatives to their corresponding epoxides and wondered whether the MTO–hydrogen peroxide system would be effective in this transformation.[6] Whilst the oxidation of enol ethers,[7a] silyl enol ethers,[7b] silyl ketene acetals[7c] and furans[7d] has been documented using this reagent combination the analogous functionalisation of more complex substrates such as carbohydrate derivatives has not been described. The recent report by Goti[7e] *et al.* prompts us to publish our results in this area.

We were gratified to find therefore that treatment of 3,4,6-tri-*O*-acetyl-D-glucal **2** with two equivalents of 30% hydrogen peroxide in the presence of a catalytic quantity of MTO in methanol for 2 h at ambient temperature afforded directly the β-D-*gluco*-pyranoside **4**[8a] and the α-D-*manno*-pyranoside **5**[8a] in 78% isolated yield (**4**:**5** = 2:1). We presume that this interconversion proceeds *via* S_N2 opening of the epoxides **3**-α,β by methanol, a reaction which may well be promoted by the presence of the rhenium catalyst which is known to act as a Lewis acid.[4] Direct conversion of the crude product from the oxidation sequence (excess Ac_2O/pyridine, rt, 12 hours; 71%) afforded the acetates **6** and **7** (**6**:**7** = 2:1) whose spectral data were compared directly with authentic samples thereby securing our stereochemical assignment. Encouraged by these initial results we investigated the epoxidation-glycosylation sequence on a variety of glycal derivatives.

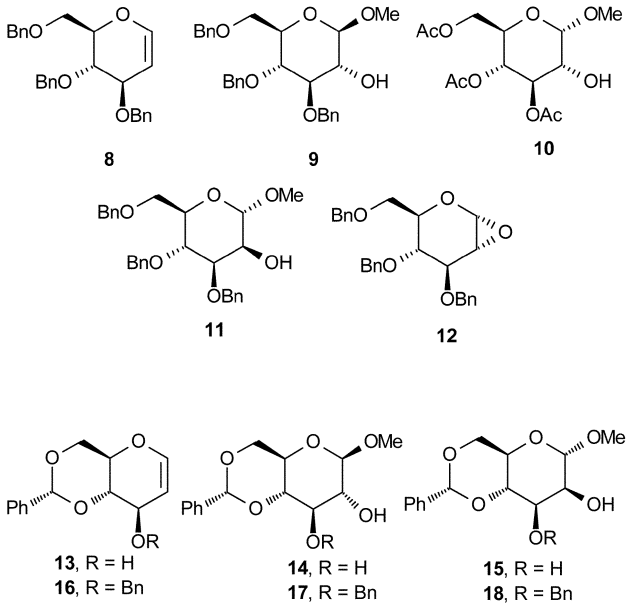


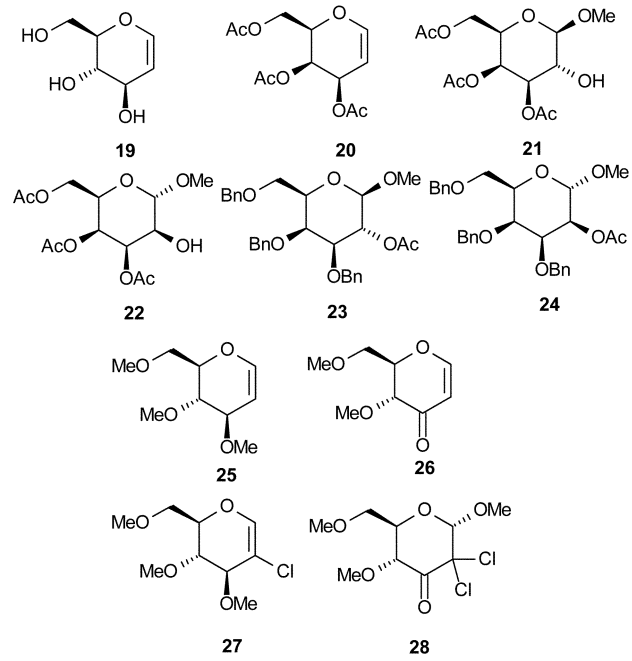
2

Changing acetate to a benzyl protecting group, as in **8**, has little effect on the overall efficiency (76% yield) of the reaction but was more stereoselective affording the β- and α-D-*gluco*-pyranosides **9**[8b] and **10**[8c] as by far the major products (**9**:**10**:**11**[8b] = 11:1:2). The generation of a small quantity of the α-D-*gluco*-pyranoside **10** in this case could arise by equilibration of the β-D-*gluco*-pyranoside **9** or may be due to an erosion of stereospecificity in the ring opening of the α-epoxide **12** as previously observed by Timmers *et al.*[9] Oxidation of the conformationally locked benzylidene acetals **13** and **16**[8d] is selective for the β-D-*gluco*-pyranosides **14** and **17**. In the case of **13**, with a free hydroxyl group at C-3, the glycosides **14**[8e] and **15**[8f] were isolated in 55% yield (**14**:**15** = 2:1) whilst **16**

Green Context

Development of greener methods for carrying out synthetic transformations often is limited to a few simple test reactions, with more complex systems being less thoroughly investigated. Here, novel clean oxidation approaches based on hydrogen peroxide are described which work well for several polyfunctional molecules. High yields and interesting stereochemical outcomes are recorded for a range of protected carbohydrates. ***DJM***





afforded **17**[8g] (61% yield) together with a trace of the alternate diastereoisomer **18**.[8h]

These results indicate that an allylic hydroxyl group has little *syn*-directing ability when the reaction is conducted in methanol, a result which is in keeping with the diastereoselectivity observed in the epoxidation of cyclohex-2-en-1-ol under similar conditions.[10] This effect is mirrored in the case of glucal **19** which on epoxidation, ring opening and peracetylation afforded a 2:1 mixture of the β-D-*gluco*-pyranoside **6** and the α-D-*manno*-pyranoside **7** in 65% overall yield. As to be expected epoxidation of 3,4,6-tri-*O*-acetyl-D-galactal **20** proceeded with a marginally greater selectivity than the corresponding glucal **2**, affording the β-D-*galacto*-pyranoside **21**[8i] and the α-D-*talo*-pyranoside **22**[8j] (**21**:**22** = 3:1) in 73% yield.

The effect of protecting group on the rate of reaction was briefly investigated using a simple competition experiment. Treatment of a 1:1 mixture of **2** and **8** to a catalytic quantity MTO (10 mol%), H_2O_2 (2 eq.) in methanol at ambient temperature for 2 h followed by aqueous work-up and acetylation of the crude reaction mixture afforded the tetracetates **6** and **7** and the monoacetates **23**[6a,8b] and **24**[8b] in 43% and 38% isolated yield respectively. The lack of discrimination observed in this reaction is presumably a reflection of the reactivity[5] of nucleophilic enol ethers towards the electrophilic oxidising agent. Surprisingly oxidation of 3,4,6-tri-*O*-methyl-D-glucal **25**, under our standard conditions, was less clean and afforded a mixture of products including the pyrone **26**[11] (*ca.* 20%) whilst the vinyl chloride **27** afforded the α-D-2,2-dichloro-2-deoxy-*gluco*-pyranoside **28** in 24% isolated yield.[12]

All of the oxidation reactions described above were conducted in homogeneous solution. Recent reports[13] suggest that the urea–hydrogen peroxide inclusion complex (UHP), a stable solid which is commercially available, can also act as a source of hydrogen peroxide in MTO oxidations even though these reactions are heterogeneous when conducted in common organic solvents. We have found that UHP can also act as an alternative to hydrogen peroxide in the oxidation of glycals. For example treatment of **2** with MTO (10 mol%) in methanol in the presence of UHP (2 eq.) at ambient temperature for 2 h afforded, after acylation, the glycosides **6** and **7** (**6**:**7** = 2:1) in 76% isolated yield, a result which is essentially identical to that obtained with hydrogen peroxide itself.

During the course of these investigations the effect of solvent on the efficiency of the epoxidation-ring opening sequence was also briefly investigated. Curiously when acetonitrile was used as solvent in the UHP oxidation of **2** the isolated yield of the methyl glycosides **4** and **5** was diminished considerably (*ca* 10% yield). Blank studies revealed that the problems associated with low turnover lay in the instability of the MTO in acetonitrile containing hydrogen peroxide. In this solvent the MTO decomposed liberating methanol and presumably perrhenate. In addition the stereochemical outcome of the reaction was reversed with the α-D-*manno*-pyranoside **5** now being the major product (**5**:**4** = 3:1). Thinking that in this solvent system at least a different oxidation pathway was operative led us to attempt the oxidation of **8** under Payne-type conditions.[2a] Indeed, exposure of **8** to H_2O_2 (30 % aq.; 5 eq.) and $KHCO_3$ (0.25 eq.) in MeOH containing acetonitrile (5 eq.) at ambient temperature for 48 h followed by a simple aqueous work up afforded the methyl glycosides **9** and **11** in 82% yield,[14] with the α-D-*manno*-pyranoside **11** predominating (*manno*:*gluco* = 3:1). In this case the allylic ether substituent exerts a different effect on the stereochemistry of the epoxidation sequence, possibly *via* the formation of a hydrogen bond between the ether oxygen and reagent, an effect which has been noted by others in the epoxidation of cyclohexene derivatives.[2b]

In conclusion we have demonstrated that either the MTO–hydrogen peroxide or hydrogen peroxide–acetonitrile systems cleanly oxidise a variety of glycals leading directly to methyl glycosides. Although not exhaustive, our preliminary results indicate that the stereochemical outcome of these reactions is complementary: Payne oxidation conditions introducing the epoxide oxygen *syn*- to the allylic oxygen whereas MTO delivers the oxygen *anti*- to the allylic oxygen (Table 1). Given the ease of operation of these reactions they should find applications in carbohydrate chemistry, an area which is currently under investigation.

Table 1 Product distribution from the oxidation of glycals

Substrate	Product	Yield (%)
2	**4** and **5** (**4**:**5** = 2:1)	78[a]
8	**9**, **10** and **11** (**9**:**10**:**11** = 11:1:2)	76[a]
13	**14** and **15** (**14**:**15** = 2:1)	55[a]
16	**17**	61[a]
19	**6** and **7** (**6**:**7** = 2:1)	65[a,b]
20	**21** and **22** (**21**:**22** = 3:1)	73[a]
25	**26**	20[a]
27	**28**	24[a]
2	**6** and **7** (**6**:**7** = 2:1)	76[c,b]
8	**9** and **11** (**9**:**11** = 1:3)	82[d]

[a] Using MTO–H_2O_2. [b] After peracylation. [c] Using MTO-UHP. [d] Using H_2O_2–MeCN.

Experimental

The oxidation of 3,4,6-tri-*O*-acetyl-D-glucal **2** is representative. To a solution of **2** (1.0 g, 3.7 mmol) in methanol (30 mL) was added MTO (9.2 mg, 3.6×10^{-2} mmol) followed by H_2O_2 (0.83 mL of 30% aq. soln., 7.4 mmol). The pale yellow solution was kept at ambient temperature for 2 h after which time water (20 mL) was added. The aqueous phase was extracted (CH_2Cl_2, 3×20 mL), the organic extracts tested for peroxide (starch-iodide paper) dried ($MgSO_4$) and concentrated *in vacuo* affording a mixture of the methyl glycosides **4** and **5** (920 mg 78% yield) in an essentially pure state.

Payne oxidation of 8

To a solution of **8** (0.84 g, 2.0 mmol) in methanol (5.0 mL) was added $KHCO_3$ (50 mg, 0.50 mmol), acetonitrile (0.53 mL, 10 mmol) and H_2O_2 (1.1 mL of 30% aq. soln., 10 mmol) and left to stir at ambient temperature for 48 h. The reaction mixture was extracted (CH_2Cl_2, 3×10 mL), the organic extracts washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to afford a mixture of the methyl glycosides **9** and **11** (770 mg, 82% yield) in an essentially pure state.

Acknowledgements

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14 We presume that acetamide is also produced as a by-product in this oxidation sequence but we were unable to verify its generation because of its water solubility.

Communication

Influence of solvent structural variations on the mechanism of facilitated ion transfer into room-temperature ionic liquids†‡

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The predominant mode of strontium ion transfer from acidic nitrate media into a series of 1-alkyl-3-methylimidazolium-based room-temperature ionic liquids containing dicyclohexano-18-crown-6 (DCH18C6) shifts from cation exchange to strontium nitrato-crown ether complex partitioning as the hydrophobicity of the ionic liquid cation is increased.

Introduction

Since the introduction of the first low-melting, air- and water-stable ionic liquids (ILs) in 1992,[1] there has been growing interest in their potential as replacements for conventional (*i.e.*, molecular) organic solvents in a host of applications in synthesis,[2–5] catalysis,[5–7] and electrochemistry.[8,9] Among the many unique properties of ionic liquids[10] is an extraordinary degree of tunability, with relatively minor changes in the structure of the constituent cation or anion frequently leading to dramatic changes in physicochemical properties.[5] Such tunability is of obvious potential utility in the application of ionic liquids in separations, and recently, there has been considerable interest in the possibilities offered by these "neoteric" solvents in various separation processes.[11–21] Of particular interest in this laboratory[22–24] have been the possibilities afforded by room-temperature ionic liquids (RTILs) in the liquid–liquid extraction of metal ions. Dai *et al.*[16] were first to suggest that the unique solvation environment offered by ionic liquids could make them especially efficient as solvents for the extraction of ionic species (*e.g.*, cationic metal complexes) from aqueous solution. In their work, remarkably large strontium distribution ratios (D_{Sr}, defined as $[Sr]_{org}/[Sr]_{aq}$ at equilibrium), far exceeding those obtainable with any conventional organic solvent, were observed in the extraction of strontium from water into solutions of dicyclohexano-18-crown-6 (DCH18C6) in any of several *N*,*N*′-dialkylimidazolium-based RTILs. In a pair of recent reports,[22,23] this enhanced extraction efficiency was shown to have its origin in differences in the mechanism of strontium ion transfer from an aqueous phase into these solvents *versus* conventional solvent systems. Specifically, for 1-alkyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl] imides (abbreviated hereafter as $C_n mim^+Tf_2N^-$) bearing a short (*e.g.*, $n = 5$) alkyl chain, exchange of the cationic strontium-crown ether complex, $Sr{\cdot}CE^{2+}$, for the cationic constituent of the ionic liquid, $C_n mim^+$, was found to represent an important mode of strontium ion transfer from aqueous nitrate solution:

$$Sr{\cdot}CE^{2+} + 2C_n mim^+_{org} \Leftrightarrow Sr{\cdot}CE^{2+}_{org} + 2C_n mim^+ \quad (1)$$

In contrast, strontium ion partitioning into conventional solvents (*e.g.*, n-alkanols) in the presence of DCH18C6 has been found[25] to proceed *via* extraction of a strontium nitrato-crown ether complex:

$$Sr^{2+} + 2NO_3^- + CE_{org} \Leftrightarrow Sr(NO_3)_2{\cdot}CE_{org} \quad (2)$$

This difference was shown to not only influence the relative cation extraction efficiency achievable with the two types of solvents, but also to have significant negative implications for the "greenness" (hence, the potential utility) of ionic liquids as extraction solvents, since increased strontium ion (and by analogy, other metal ion) partitioning into the ILs will be accompanied by increased solubilization of the ionic liquid in the aqueous phase,[22] a clearly undesirable result.

Obviously, as the hydrophobicity of the IL cation is increased, cation exchange should become increasingly difficult and in fact, decreased strontium partitioning has been observed as the length of the alkyl chain (*i.e.*, *n* in $C_n mim^+$) is increased.[22] It thus seems reasonable to expect that for an IL incorporating a sufficiently hydrophobic cation, the ion-exchange mechanism would no longer be viable and that for such ionic liquids, the predominant mode of metal ion partitioning would revert to that observed for a conventional organic diluent. To explore this possibility, we have employed a combination of radiometric, chromatographic, and X-ray absorption fine structure (EXAFS)

Green Context

The level of research activity in ionic liquids continues to increase and while we see an expansion in the potential applications for these interesting substances, it is important that we improve our understanding of their behaviour. This article represents a step towards an improved understanding of the fundamental aspects of facilitated ion transfer into room temperature ionic liquids. This has significant practical implications in the areas of separation and catalysis. Importantly, it demonstrates that ion exchange need not be the sole mode of cation transfer in these liquids. ***JHC***

† Electronic supplementary information (ESI) available: lengths of the average scattering paths and the Debye–Waller factors for the Sr–C and Sr–C–O paths. See http://www.rsc.org/suppdata/gc/b3/b310507p/

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measurements to examine the extraction of strontium from acidic nitrate media by DCH18C6 in a series of 1-alkyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl] imides. Comparison of the results obtained for a long-chain (*n*-decyl) compound to those observed for an analogous short-chain (*n*-pentyl) compound and for a conventional aliphatic alcohol (*n*-octanol) provides insight into the process of cation partitioning into $C_{10}mim^+Tf_2N^-$ and the factors governing the mechanism of facilitated ion transfer into imidazolium-based RTILs.

Experimental

Materials

The ionic liquids were prepared and purified according to published methods.[26] Unless otherwise noted, for partitioning studies, the DCH18C6 (Aldrich, Milwaukee, WI) was a mixture of the *cis–syn–cis* and *cis–anti–cis* isomers, consistent with prior work.[16,22] For EXAFS measurements, only the *cis–syn–cis* isomer (Acros Organics, Pittsburgh, PA) was employed, so as to facilitate interpretation of the results.

Methods

All strontium distribution ratios were determined radiometrically using a commercial Sr-85 radiotracer (Isotope Products Laboratories, Burbank, CA), assayed *via* gamma spectroscopy using standard procedures.

For the Sr K-edge X-ray absorption measurements, the liquid samples in C_6mim^+-, C_8mim^+-, and $C_{10}mim^+Tf_2N^-$ were placed in 6 mm I.D. polyethylene tubes. Data were collected in the fluorescence mode at the Advanced Photon Source Beamline 12-BM.[27] The EXAFS signal was extracted and analyzed using IFEFFIT.[28] A single scan of each sample produced a useful k^3-weighted EXAFS signal between 2.25 and 11.0 $Å^{-1}$. The samples were sufficiently dilute that corrections for self-absorption were not required. The phase and amplitude functions used to fit each set of experimental data were calculated by FEFF8.00[29] from the atomic positions of $Sr(NO_3)_2$(18-crown-6). Only the most important scattering paths generated by the FEFF calculation were considered, the single scattering Sr–O and Sr–C paths and the three legged Sr–O–C multiple scattering path. The k^3-weighted EXAFS were fit in *R*-space (ΔR = 1.5–4.3 Å) to the FEFF paths fixing the amplitude reduction factor S_0^2 = 1.0, and using a single, variable threshold energy shift (ΔE_0). The coordinated O atoms were treated as a single shell of variable coordination number with its Debye–Waller factor (σ^2) fixed at 0.0136, as previously determined for Sr-crown ether complexes.[23] The coordination number of the crown ether C atoms was fixed at 12, but the Debye–Waller factor was allowed to vary, as were all of the average scattering pathlengths, which gave 7 floating parameters in the fit (maximum allowed = 16). The previously calculated uncertainty in σ^2 of the O shell (0.0010) was combined with the calculated error estimates of N_O, to give an estimated total uncertainty in N_O. (The lengths of the average scattering paths and the Debye–Waller factors for the Sr–C and Sr–C–O paths are available as electronic supplementary information†).

Results and discussion

Table 1 summarizes the results of measurements of the partitioning of strontium and nitrate ions between water and a series of $C_nmim^+Tf_2N^-$ ionic liquids in the presence of DCH18C6. For the *n*-pentyl compound, the amount of nitrate extracted is far less than the amount of extracted strontium ion, and is thus vastly insufficient to produce a neutral strontium nitrato-crown ether complex. As the alkyl chain length is increased, however, nitrate co-extraction becomes increasingly significant, consistent with a shift from cation exchange to extraction of the neutral complex. For the *n*-decyl compound, in fact, the amount of nitrate extracted is exactly that expected if extraction of the neutral complex were the sole mode of strontium ion partitioning.

Table 1 Strontium[a] and nitrate[b] ion partitioning between water[c] and solutions of DCH18C6[d] in $C_nmim^+Tf_2N^-$

Organic phase mode	$\%E_{Sr}$	$\%E_{NO_3^-}$[e]	Partitioning indicated
$C_5mim^+Tf_2N^-$	96.5	9 ± 7[f], 16[fg]	cation exchange
$C_6mim^+Tf_2N^-$	82.6	16.1 ± 0.8	cation exchange
$C_8mim^+Tf_2N^-$	39.0	20.9 ± 1.0	mixed
$C_{10}mim^+Tf_2N^-$	20.2	20.0 ± 1.0	extraction of neutral complex

[a] Determined radiometrically. [b] Determined by ion chromatography, unless otherwise noted. [c] Containing 0.0310 M $Sr(NO_3)_2$. [d] 0.202 M *cis-syn-cis* DCH18C6 in the indicated ionic liquid. [e] For partitioning *via* extraction of the neutral strontium nitrato-crown ether complex only, the percentage extraction of nitrate ion should correspond to $\%E_{Sr}$. For partitioning *via* cation exchange, no nitrate co-extraction ($\%E_{NO_3^-}$ = 0) is expected. [f] As reported in reference 23. [g] Determined by N-15 NMR.

Additional evidence of a shift in the mechanism of partitioning with IL cation hydrophobicity is presented in Fig. 1, which

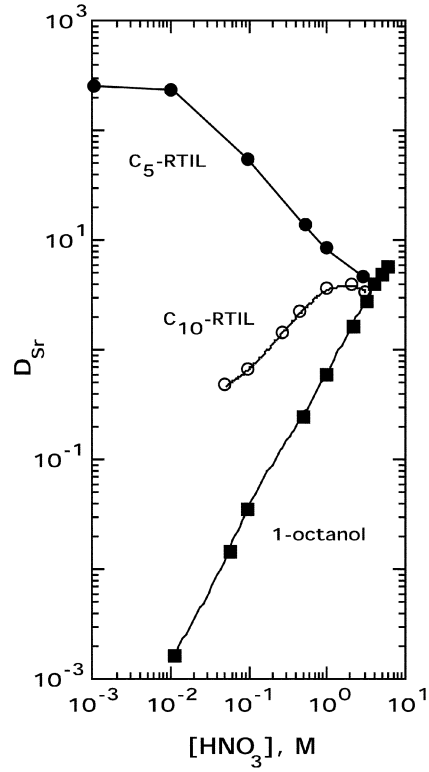

Fig. 1 Nitric acid dependency of D_{Sr} for DCH18C6 (0.10 M) in 1-octanol, $C_5mim^+Tf_2N^-$, and $C_{10}mim^+Tf_2N^-$. (T = 23 °C).

depicts the dependency of D_{Sr} on nitric acid concentration for solutions of DCH18C6 in 1-octanol, $C_5mim^+Tf_2N^-$, and its C_{10} analog. For $C_5mim^+Tf_2N^-$, increasing acidity is accompanied by a decrease in strontium partitioning, an observation which, as noted previously for $C_2mim^+Tf_2N^-$,[22] is consistent with ion exchange as a mode of ion transfer. In contrast, for both 1-octanol and $C_{10}mim^+Tf_2N^-$, increasing nitric acid (hence, nitrate ion) concentration in the aqueous phase is accompanied by an increase in D_{Sr}. (Note that the leveling off of D_{Sr} at the highest acidities in the IL is the likely result of decreased free

DCH18C6 concentration arising from nitric acid extraction by the crown ether, as has been observed previously.[30]) As is the case for 1-octanol[25] then, the mechanism of strontium ion partitioning into $C_{10}mim^+Tf_2N^-$ must involve extraction of the neutral strontium nitrato-crown ether complex. Thus, just as relatively minor variations in the nature of the cation or anion comprising an IL can lead to dramatic changes in its physicochemical properties, so too can such variations lead to a significant change in the mechanism of ion transfer into these solvents.

To obtain further insight into the nature of the extracted species in each system, the total number of oxygen atoms, N_O, and the number of nitrate anions coordinated to strontium were determined for the complex extracted into each of four *N,N*-dialkylimidazolium bis[(trifluoromethyl)sulfonyl] imides ($C_nmim^+Tf_2N^-$, with n = 5, 6, 8, and 10) *via* EXAFS measurements (Table 2 and Fig. 2) and the results compared to

Table 2 Average total number of oxygen atoms or nitrate anions coordinated to strontium derived from EXAFS measurements

Solvent	N_0	Coordinated NO_3^-/Sr^a
1-Octanol[b]	10.2	2.1
$C_5mim^+Tf_2N^-$[b]	8.5	0.3
$C_6mim^+Tf_2N^-$	7.9	0 ± 0.7
$C_8mim^+Tf_2N^-$	8.4	0.2 ± 0.5
$C_{10}mim^+Tf_2N^-$	8.6	0.3 ± 0.5

[a] Assuming a hexacoordinate crown ether, bidentate NO_3^- coordination, and two axial ligands. [b] From reference 23.

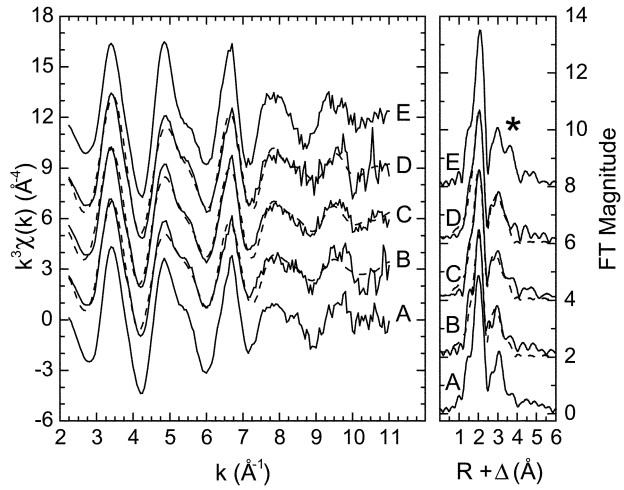

Fig. 2 Sr K-edge EXAFS (—) and best fit (**---**) of the Sr–DCH18C6 complexes present in 1-octanol and various $C_nmim^+Tf_2N^-$ solutions (offset vertically). (**A**) $Sr(DCH18C6)^{2+}$ in $C_5mim^+Tf_2N^-$,[23] (**B**) $Sr(DCH18C6)^{2+}$ in $C_6mim^+Tf_2N^-$, (**C**) $Sr(DCH18C6)^{2+}$ in $C_8mim^+Tf_2N^-$ (**D**) $Sr(DCH18C6)^{2+}$ in $C_{10}mim^+Tf_2N^-$ (**E**) $Sr(NO_3)_2(DCH18C6)$ in 1-octanol.[23] The position of the peak characteristic of the Sr-distal nitrate oxygen scattering is marked with a star. Fourier transforms are not phase shift corrected.

those obtained previously for 1-octanol.[23] When $Sr(NO_3)_2(DCH18C6)$ is extracted into 1-octanol, three major peaks are evident in the Fourier-transformed EXAFS: a peak corresponding to 10 oxygen atoms (six crown ether O atoms and four O atoms from two axially-coordinated bidentate nitrate groups) at 2.7 Å, a second peak corresponding to 12 crown ether carbon atoms at 3.5 Å, and a third peak for the two distal (uncoordinated) oxygen atoms of NO_3^- at 4.3 Å. Thus, in the extracted complex, strontium is 10-coordinate and two nitrate ions are present in the inner coordination sphere.[23] In contrast, the absence of the distal oxygen peak in the EXAFS of all the RTIL samples indicates that no detectable amount of nitrate is directly coordinated to strontium in any of the RTILs, even for $C_{10}mim^+Tf_2N^-$. Because the ion chromatographic results for this IL clearly demonstrate that two nitrate ions are co-extracted with the $Sr(DCH18C6)^{2+}$ moiety, these ions must be present in the outer coordination sphere, forming outer-sphere ion pairs with solvated $Sr(DCH18C6)^{2+}$ cations in $C_{10}mim^+Tf_2N^-$. In this respect, the complex extracted into $C_{10}mim^+Tf_2N^-$ resembles the strontium nitrate complexes of triethanolamine[31] and the azacrown 2,6-pyridinedicarboxylic tetra(ethylenegycol) diester,[32] in which nitrate ions lie outside of the inner coordination sphere.

Conclusions

The results of this study, in addition to representing a step toward an improved understanding of the fundamental aspects of facilitated ion transfer into room-temperature ionic liquids, have significant practical implications in the areas of separations, catalysis, and green chemistry. For example, catalytic processes dependent upon anion transfer (*e.g.*, oxidation of alkenes by permanganate) would be expected to exhibit higher efficiency in RTILs into which (unlike $C_5mim^+Tf_2N^-$) anion extraction is facile. From the perspective of separations, more efficient anion coextraction implies more facile recovery of extracted metal ions. For DCH18C6/$C_{10}mim^+Tf_2N^-$, for example, strontium partitioning is readily controlled by simply adjusting the aqueous nitrate ion concentration, as in a conventional solvent system.[33] Finally, as we have noted previously,[22] IL-based extraction systems for which the predominant mode of ion transfer involves the concomitant loss of the cationic constituent of the ionic liquid to the aqueous phase clearly cannot be regarded as "green", particularly on the process (*i.e.*, hydrometallurgical) scale. The results presented here, by demonstrating that ion exchange need not be the sole mode of cation transfer into an ionic liquid, thus offer renewed hope that practical, environmentally benign metal ion separation systems employing these solvents can be developed.

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Communication

Recycling in telomerization of butadiene with methanol and phenol: Pd–KF/Al_2O_3 as an active heterogeneous catalyst system

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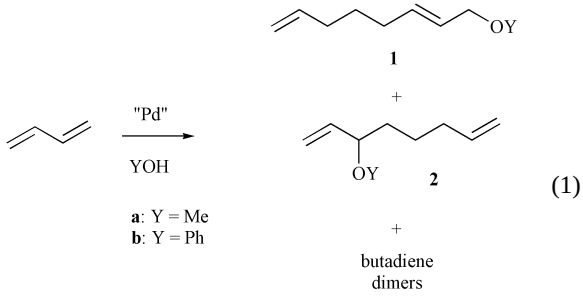
A palladium-TPPTS catalyst heterogenized on KF/alumina has been shown to be effective and recyclable for the telomerization of butadiene with methanol and phenol. The initial catalytic system is modified during the first run, allowing its stabilisation and improving its activity.

Although low amounts of palladium based catalysts are generally sufficient to achieve the telomerization of butadiene with nucleophiles,[1–3] the cost of the metal urges the development of recyclable systems. Several approaches have been proposed for telomerization recycling. A metal catalyst anchored on a polymer matrix bearing different types of ligands[4–6] could be easily recovered and reused with some loss of activity[4,5] or with its preservation.[6] Activity in telomerization was observable after heterogenization of the metal on macroporous support and addition of phosphane,[5,6] but some leaching of the metal strongly decreased the recycling efficiency. In fact, the choice of the support seemed to be crucial in regard to the activity preservation since palladium anchored on montmorillonite could be recycled without loss of activity and selectivity in telomerization of butadiene with water, contrary to palladium on charcoal where a fast decrease was observed, and palladium on alumina where the reactivation of the support was required.[7] Another alternative to obtain recycling systems was the use of ionic liquids as supplier of a recoverable and reusable homogeneous medium.[8] The solubilisation of the palladium in water thanks to TPPTS as ligand allowed recovery of the catalyst in the aqueous phase when the telomerization was achieved in a biphasic system.[9] In a classical homogeneous medium, we have reported that the use of the 15-membered macrocyclic triolefin **Ma** as ligand (Fig. 1) allowed recovery of an active stabilized **Pd–Ma** catalytic system.[10,11] The process was efficient with methanol as nucleophile (eqn. 1), since the



reaction products were recovered by distillation at relatively low temperature. In contrast, the high boiling point adducts obtained with phenol as the nucleophile were difficult to extract from the medium without damaging the catalyst. In order to facilitate the catalyst recovery, we turned our efforts to heterogeneous systems. Using a Pd-phosphane catalyst immobilised on silica under "supported aqueous" phase conditions, Sinou *et al.* have reported effective Tsuji–Trost allylic substitutions without loss of activity.[12] Here, we present our results on the telomerization of butadiene with methanol and phenol using palladium immobilised on mesoporous supports as catalysts.

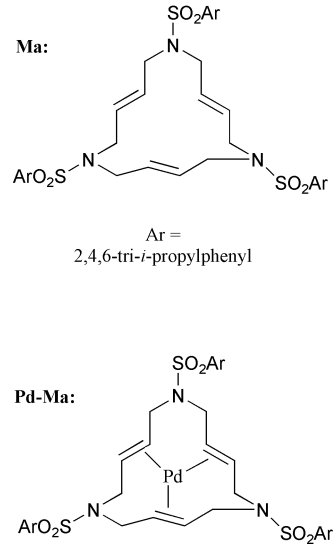


Fig. 1 Structures of the Pd-catalyst and macrocyclic ligand.

Green Context

The telomerization of butadiene is a good example of an atom efficient reaction. The feedstock is inexpensive, the reaction can be 100% atom efficient and the products are valuable. The main problem with existing processes is the need for expensive palladium catalysts. When homogeneous, these can be, at least in part, lost while heterogeneous analogues have previously been unsatisfactory. Here a novel solid catalyst system is shown to be active, recoverable and recyclable. ***JHC***

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Experimental

Preparation of the catalyst $Pd^0(TPPTS)_n$/support

An application of the procedure[12] described from $Pd(OAc)_2$ was used with the following supports: Silica (Kieselgel 60, 0.04–0.063 mm from Merck), Montmorillonite K10 (Fluka), Al_2O_3 (Merck 90, 0.063–0.2 mm) and KF/Al_2O_3, prepared as described.[13] KF was from Acros and $P(C_6H_4\text{-}m.SO_3Na)_3$ (TPPTS) from Rhodia (TPPTS contains 10–20% of oxidised phosphane OTPPTS as indicated by NMR. Thus equivalents of this compound were calculated taking this fact into account).

A solution of palladium acetylacetonate (76.2 mg, 0.25 mmol), TPPTS (1.25 mmol, 888 mg) in degassed water (3 mL) is stirred at room temperature for 2 h, then transferred under argon to a Schlenk tube containing the support (2 g, previously activated by heating at 170 °C/10^{-2} mm Hg for 12 h). After stirring the suspension for 2 h followed by evaporation of the water (10^{-2} mm Hg, gentle heating), the collected yellow powder is handled under a flow of argon.

Telomerization experiments

Methanol as nucleophile. The catalytic system (2.5×10^{-2} mmol of Pd, calculated from starting $Pd(acac)_2$) is introduced in an autoclave equipped with a magnetic stir bar. After three purges of "vacuum-argon", the degassed solution of MeOH (1.5 mol, 6 mL) and nonane (internal GC standard, 128 mg) is introduced under argon. The autoclave is cooled to −20 °C in a bath of acetone–liquid nitrogen. Butadiene (1 mol, 9 mL), condensed at −20 °C in a Schlenk tube, is carefully transferred into the autoclave under argon. The latter is then heated in an oil bath at 60 °C for the time mentioned in Table 1. At the end of the reaction, the autoclave is cooled to room temperature and carefully opened under a hood (possible butadiene emanations). The products are recovered by distillation at 40 °C under reduced pressure (10^{-2} mm Hg) and analysed by GC.

Phenol as nucleophile. The methanol of the above procedure is replaced by a degassed solution of phenol in acetone (see relative amounts of reactants in Table 2). Under these conditions, the reaction products are extracted by filtration under argon, followed by washing of the solid with acetone (3 × 10 mL).

Recycling procedure

After extraction of the reaction products, the resulting solid residue is dried under vacuum (10^{-2} mm Hg, 2 h at RT) and reused without further treatment.

Table 2 Use of the $Pd(TPPTS)_n$–KF/Al_2O_3 system in the telomerization of butadiene with phenol[a]

Entry	Run	Time/min	TON	Phenol[b] conv. (%)	Selectivity (%)		
					1b	**2b**	Dimers
1	1	120	26	29.5	51[c]	3	34
	2	128	88	100	92	4	4
	3	124	86	97	86	7	7
	4	120	84	95.5	84	8	8
	5	120	85	96.5	94	3	3
	6	125	71	80.5	94	3	3
	7	118	88	100	92	4	4
	8	123	82	93	96	3	1
2	1[d]	125	50	28.5	91[b]	2	6
	2[e]	121	102	58	91	4	5
	3	120	169	95.8	92	5	3
	4	120	165	94	95	3	2

[a] Pd : PhOH : butadiene: 1 : 88 : 176, Pd (2.5×10^{-1} mmol), acetone (5 mL), 60 °C. [b] Phenol is the limiting substrate here. [c] Small amounts of 1-phenoxy-2-butene and 3-phenoxy-1-butene have also been detected. [d] Pd : PhOH : butadiene: 1 : 176 : 352. [e] From this run, the catalyst was handled under air without special precaution.

Results

Different supported catalysts have been prepared and their efficiency in telomerization of butadiene with methanol and phenol as their recycling ability have been examined.

Telomerization with methanol

The results with montmorillonite, silica and KF/alumina as supports are reported in Table 1. The most active and selective system is $Pd(TPPTS)_n$/montmorillonite but it quickly lost its efficiency (Entry 1). The activity of $Pd(TPPTS)_n$/silica increases during the first recycling but has completely deteriorated in the second one (Entry 2). The best preservation of activity and selectivity for the linear telomer is observed when the palladium catalyst is heterogenized on KF/alumina (Entry 3).

Telomerization with phenol

Switching to phenol as nucleophile, the above results led us to pursue our studies with palladium supported on KF/Al_2O_3. We were delighted to observe a great stability of the catalyst system (Table 2). Phenol is more sluggish than methanol to react and the palladium concentration was increased to about 1% in the first set of experiments (Entry 1) and the half in the second (Entry 2). The catalyst is less reactive and selective during the first run compared to the subsequent runs; furthermore the

Table 1 Efficiency of various $Pd(TPPTS)_n$/supports in telomerization of butadiene with methanol[a]

Entry	Support	Run	TON	Butadiene conv. (%)	Selectivity (%)		
					1a	**2a**	Dimers
1	montmorillonite	1	720	36	78	4	18
		2[b]	320	16	82	6	12
		3[b]	40	2	71	1	28
2	silica	1	460	23	70	10	20
		2[b]	620	31	75	20	5
		3[b]	0	0	0	0	—
3	KF/Al_2O_3	1	360	18	70	4	26
		2[b]	440	22	68	6	26
		3[b]	320	16	73	4	23
		4[b]	360	18	71	5	24

[a] Pd : MeOH : butadiene: 1 : 6000 : 4000, 60 °C, 1 h. [b] Reuse of the preceding Pd-supported catalyst.

Table 3 ^{31}P NMR investigations

Observed → / Conditions ↓	$Pd(acac)_2L_2$ δ (ppm)	OTPPTs δ (ppm)	PdL_2 δ (ppm)	PdL_3 δ (ppm)	PdL_4 δ (ppm)	Observations
$Pd(acac)_2$ + 2 L, D_2O[a]	36.60	35.81	24.23 (s)	n.o.[c]	n.o.[c]	Pd black after one hour.
$Pd(acac)_2$ + 3 L, D_2O[a]	36.62	35.80	n.o.[c]	18.58 (br)	n.o.[c]	Pd black after one day.
$Pd(acac)_2$ + 4 L, D_2O[a]	36.74 (weak)	35.75	n.o.[c]	n.o.[c]	8.60 (br)	Shift to 24.20 (1day) then Pd black.
$Pd(acac)_2$ + 5 L-KF/Al_2O_3, D_2O[b]	n.o.[d]	35.86	24.18 (s)[e]	18.22 (s)[e]	n.o.[c]	additional signal at 22.05 (s).[e]
As above after 4 runs, D_2O	n.o.[d]	35.84	n.o.[d]	18.21	n.o.[c]	22.04 (s), 28.90 (s).[f]
$Pd(acac)_2$ + 5 L-KF/Al_2O_3, solid phase	n.o.[c]	Broad signals between 20–35 ppm, 5–20 ppm, andone centred at – 8 ppm				
As above after 3 runs, solid phase	n.o.[c]	Unique broad signal between 9–38 ppmwith a maximum at 20 ppm				

[a] Palladium precursor and L (TPPTS) are dissolved in degassed D_2O and spectra recorded after 10–20 min. [b] The supported catalyst is prepared as described, dried and dissolved in degassed D_2O and spectra immediately recorded. [c] Not observed. [d] Not observed or as traces depending on the batch. [e] The intensity of the signal around 24 ppm increased with time to the detriment of both signals at 18 and 22 ppm. [f] Weak signal, which could be attributed to a Pd complex bonded to one of the reactants.

production of small amounts of phenoxybutene is noticed. These observations could be related to a modification of the catalyst system during the first run. In using different batches of catalysts, we observe slight differences of the results but similar behaviour. Consumption of phenol became complete or almost complete after 1 or 2 runs and the selectivity for the linear telomer was high (> 18/1). The catalyst remained active, even when handled under air atmosphere (Entry 2, run 2). Interestingly, eight successive runs have been carried out with the same catalytic system, without loss in either selectivities or activities.

NMR studies

After dissolution of $Pd(acac)_2$ in carefully degassed D_2O and addition of increasing amounts of TPPTS (abbreviated as L), we have been able to characterise different phosphorus species by ^{31}P NMR analysis (Table 3). The phosphorus chemical shift of $Pd(acac)_2L_2$ is lower compared to that of $Pd(OAc)_2L_2$[12,14,15] (36.6 instead of 29.5). The low valence Pd species and OTPPTS exhibit chemical shifts close to the literature values;[12,14–16] PdL_2 and PdL_3 are not stable in solution since Pd black precipitates were observed in one hour and one day, respectively. It is interesting to note the evolution of PdL_4 to PdL_2 as shown by shifting of the signal from 8.6 to 24.2 ppm in one day, before the precipitation of metallic palladium, which is thus delayed for 2 or 3 days. The analysis in D_2O of the heterogenized catalyst prepared with 5 equiv. of TPPTS [one equiv. is consumed for the reduction of Pd(II)] afforded only the signals corresponding to PdL_2 and PdL_3 beside a new singlet at 22.05 ppm which could be attributed to a PdL_2 species in interaction with KF (as $(KF)PdL_2$, $(KF)_2PdL_2$, or aggregates) as previously proposed in the presence of lithium halides.[17] This signal and that of PdL_3 (at 18.22 ppm) decreased with time, while the signal of PdL_2 (about 24.2 ppm) increased; these modifications could be related to a desorption of the above "KF,PdL_2" species or/and to a change in the equilibrium PdL_2–PdL_3. After use of this catalyst for 4 successive runs, NMR in D_2O of the catalyst exhibit again the signals of OTPPTS, "KF,PdL_2" and PdL_3; under these conditions PdL_2 signal is minor or not observed. The same heterogenized catalyst analysed in the solid phase before use provided the signals of all species: free L at −8 ppm, PdL_n (n = 3, 4) between 5 and 20 ppm, PdL_2 superimposed on OTPPTS between 20 and 35 ppm. After one or several runs, the signals corresponding to free L and PdL_n disappeared while the massif at 20–35 ppm remained. These NMR studies led us to conclude that the heterogenization of Pd species allows the stabilisation of an active PdL_2–PdL_3 catalyst, which is probably desorbed to mediate the telomerization in solution and recovered by the support after running.

In conclusion, we have developed an efficient heterogeneous Pd-TPPTS–KF/Al_2O_3 catalyst system, in telomerization reactions of butadiene with different nucleophiles. The system is easy to recover and reuse many times, without loss of its activity. Under the conditions described, the heterogeneous support behaves as the macrocycle **Ma** in solution, trapping and stabilising an active low valence-palladium species.[10,11]

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Communication

Microwave-assisted solvent-free instantaneous Claisen rearrangement for synthesis of bis(3-allyl-4-hydroxyphenyl) sulfone

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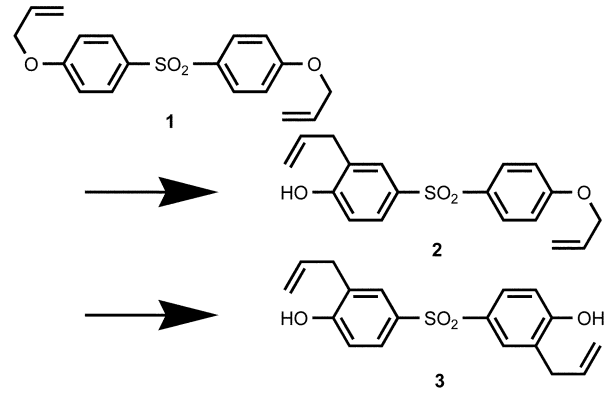
Solvent-free Claisen rearrangement of bis(4-allyloxyphenyl) sulfone (**1**) under microwave irradiation for 5 min gave high yields of bis(3-allyl-4-hydroxyphenyl) sulfone (**3**), which has been synthesized up to now under conventional heating for 2–30 h as a color developer for a heat- or pressure-sensitive recording in industry.

Introduction

Ideal industrial chemical processes require energy saving, high conversion, high selectivity, and solvent-free reaction conditions with minimizing the processes themselves. A microwave (MW, frequency 2.45 GHz) heating technique should be a promising candidate, replacing conventional boilers because microwave-assisted organic syntheses can lead to large reductions in reaction time and to enhancement in conversion and selectivity compared to conventional heating.[1–4] These microwave effects could be attributed to the characteristic heating modes of MW through the interaction of oscillating electric and magnetic fields with ordered assemblies of polar molecules expressed as dielectric loss, leading to unusual phenomena called superheating[5] or hot-spots.[6] Instantaneous heat release at the molecular level should favorably induce some thermal reactions between molecules which form a polar charge transfer state or a polar transition state as often observed in photo-induced chemical reactions. However, only a few applications of microwave heating techniques to industrial organic chemical processes have been found compared to the large number of lab-scale applications of MW.[7]

We demonstrate here a solvent-free preparation of bis(3-allyl-4-hydroxyphenyl) sulfone (**3**) under microwave irradiation under normal pressure, which has been used as a color developer for a heat- or pressure-sensitive recording in industry.[8,9] Bis(allyl hydroxyphenyl) sulfone **3** has been synthesized by Claisen rearrangement of bis(4-allyloxyphenyl) sulfone (**1**) at 481–532 K for 2–30 h in organic solvents, such as trichlorobenzene,[8] diphenyl ether[10] and 1-octanol,[11] or from Claisen rearrangement of bis(allyl ether) **1** at 468–483 K for 6 h under solvent-free conditions.[9,12] Claisen rearrangement of bis(allyl ether) **1** occurs *via* 2 step reactions: the first step reaction is a rearrangement of bis(allyl ether) **1** to 3-allyl-4-hydroxy-4′-allyloxydiphenylsulfone (**2**) and the second step is a rearrangement of **2** to **3** (Scheme 1).

In this work, we synthesize bis(3-allyl-4-hydroxyphenyl) sulfone (**3**) with a high conversion of 87% based on success in the solvent-free Claisen rearrangement of bis(4-allyloxyphenyl) sulfone (**1**) at 553 K for only 5 min under microwave irradiation under normal pressure, aiming especially at the industrial application of MW-assisted chemical processes.



Scheme 1 Claisen rearrangement of **1**.

Results and discussion

At 503 K the conversion of bis(allyl ether) **1** to bis(allyl hydroxyphenyl) sulfone **3** reached 37% after 30 min microwave

Green Context

Traditional batch processes in fine chemical manufacturing suffer from several problems including limited flexibility, typically long reaction times and often poor energy utilisation. The increasing use of more flexible flow systems based on short reaction times and high energy intensities is an important part of green chemical technology.

Here the solvent-free, instantaneous synthesis of a sulfone is described. Reaction efficiencies are high. ***JHC***

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irradiation and 76% after 60 min (entries 2 and 3, Table 1). At high temperatures above 503 K, the conversions more than 76% to **3** were achieved in 30 min at 513 K, 20 min at 523 K, 10 min at 533 K and 5 min at 543–553 K (entries 5, 7, 9–11, Table 1). The compositions of the reaction mixtures of **1, 2** and **3** were plotted against the reaction temperatures (for 5 min) in Fig. 1. From Fig. 1, the conversion to **3** monotonously increased in the temperature range from 503 K to 553 K. Giguere *et al.*[13] and Strauss *et al.*[14] reported maximum conversions of 21% and 56% for the microwave-driven Claisen rearrangement of allyl phenyl ether to 2-allylphenol at 598–634 K for 10 min when neat using a pressure tube and at 473 K for 1 h in aqueous solution using a microwave batch reactor (MBR), respectively. In this experiment, the maximum conversion to bis(allyl hydroxyphenyl) sulfone **3** was found to be 87% at 553 K for only 5 min under microwave irradiation without pressurized conditions, which was close to the conversion, 89.7%, reported in a patent using conventional heating at 468–483 K for 6 h.[12] To compare our results obtained by MW to a conventional reaction carried out at 543 K, we used a tetraethylene glycol bath (543 K) as the heat source, but we could not maintain the reaction temperature at 543 K resulting in a "thermal run away" of the reaction system because this reaction was exothermic. We reached the conclusion that MW heating is beneficial not only for shortening the reaction period by a factor of 72 but also for precise manipulation of reaction temperatures especially for exothermic reactions due to its molecular-level coherent heating mode.

We estimated the energy consumptions of the reactions in conventional heating and in microwave heating for the reaction systems and scales we employed for the experiments. The heating mode of the conventional heating reaction from 433 K to 553 K was as follows: heated at 125 W for 740 s to raise the temperature from 433 K to 493 K, heated at 252 W for 375 s from 493 K to 553 K, and heated at 252 W for 300 s to keep the temperature at 553 K (at 2/5-on and 3/5-off mode during this period). Therefore, the energy consumption of the whole process was calculated as 217 kJ from the consumed electric power during the process. The heating mode of the microwave heating reaction was as follows: irradiated at 125 W MW power for 120 s from 433 K to 533 K, and irradiated 100 W MW power for 300 s to keep the temperature at 553 K (microwave was irradiated at 1/2-on and 1/2-off mode during this period). Therefore, the energy consumption was calculated as 45 kJ. As a result, the energy consumption of the MW reaction process was estimated to need only 21% of that for the conventional heating reaction, therefore, microwave heating would save 79% of the energy required for the conventional heating reaction process.

In conclusion, we succeeded in preparing bis(3-allyl-4-hydroxyphenyl) sulfone (**3**) by microwave-assisted Claisen rearrangement of bis(4-allyloxyphenyl) sulfone (**1**) at 553 K for only 5 min without using any solvent under normal pressure. We achieved a conversion 87% for only 5 min under microwave heating which is practically high enough for industrial processes, and established foundations for a solvent-free industrial chemical process under microwave heating. In the concept of green chemistry, we believe that a large batch reaction process for the conventional industrial preparation of bis(3-allyl-4-hydroxyphenyl) sulfone (**3**) will be replaced by a compact microwave-assisted continuous flow reaction process under solvent-free conditions in the near future.

Experimental

MW irradiation experiments were performed using a multimode MW apparatus (Micro Denshi MMG-213VP, 2.45 GHz). A thermocouple (Chino, SUS316-sheathed K type, 33 cm × 1.6 mm) was inserted into the reaction solution for controlling the reaction temperatures by repeated on–off MW irradiation. A three stub tuner was used to achieve optimal MW power absorption with a forward and reverse power monitor.

In a typical experiment, a solid bis(4-allyloxyphenyl) sulfone (**1**, 10 g, mp 424–425 K[10]) in a 100 ml three-necked quartz flask was preheated to convert into a liquid at 433 K by heating in an oil bath. The liquid of bis(allyl ether) **1** at 433 K was heated to 553 K under MW (125 W) irradiation within 2 min under nitrogen atmosphere. The solution was maintained at 553 K for 5 min under repeated on–off MW (100 W) irradiation. After the MW irradiation, the solution was cooled down immediately by an air blower.

In conventional heating, we used tetraethylene glycol (Kanto Kagaku, 250 ml) heated by an electric heater (Hakko, SAA1105, max. 500 W) in a Dewar-type stainless vessel (Yazaki Kagaku, S-0, max. 432 ml) as the heat source. Temperature of tetraethylene glycol was controlled by a temperature controller (As One, T-450) using a thermocouple. Liquid bis(allyl ether) **1** (10 g) previously heated to 433 K was placed in a three-necked flask and the flask was immersed in the tetraethylene glycol bath previously heated to 543–553 K.

To determine the compositions of **1, 2** and **3** after microwave irradiation, the reaction mixtures were analyzed by high-performance liquid chromatography (HPLC, Hitachi L-7000) with Nucleosil 5C18 column (25 cm × 4.6 mm) and UV detection at 254 nm. The elution (methanol/water = 70/30, v/v) was flowed at a rate of 0.7 mL min^{-1}. The HPLC retention times were 7.9, 11.6 and 16.5 min for **3, 2** and **1**, respectively.

Table 1 Solvent-free Claisen rearrangement of **1** at 503–553 K under microwave irradiation

			Conversion (%)[a]		
Entry	Temp/K	Time/min	**1**	**2**	**3**
1	503	5	82	16	1
2	503	30	15	44	37
3	503	60	1	16	76
4	513	5	57	35	6
5	513	30	1	15	76
6	523	5	13	43	41
7	523	20	< 1	7	81
8	533	5	7	34	54
9	533	10	1	10	83
10	543	5	1	13	77
11	553	5	< 1	2	87

[a] Determined by HPLC analysis.

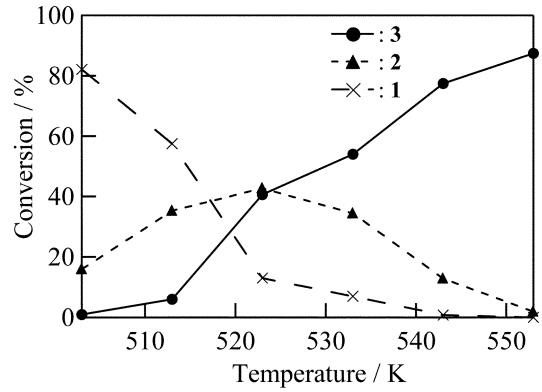

Fig. 1 Conversions of **1, 2** and **3** by solvent-free Claisen rearrangement of **1** at 503–553 K for 5 min under microwave irradiation. Conversions were determined by HPLC analysis.

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Ultrasound promoted acetylation of alcohols in room temperature ionic liquid under ambient conditions

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The *O*-acetylation of alcohols with acetic anhydride to the corresponding esters has been achieved in excellent isolated yields in short reaction time at ambient conditions under ultrasonic irradiation in the absence of any added catalyst using a room temperature ionic liquid as the medium as well as a promoter for the reaction. The products could be isolated by distillation or selective extraction from the non-volatile ionic liquid, which could be recycled giving rise to a process with minimal waste.

Introduction

The use of ultrasound in organic transformation is now well known to enhance reaction rates and yields/selectivity of reactions, and in several cases facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure.[1,2] The driving energy is provided by cavitation, the formation and collapse of bubbles, which liberates considerable energy in short times. It follows then that the molecules that can be activated for sonochemical transformation are those that can penetrate the atmosphere of the bubble, which in turn constitutes a limitation for the method. This limitation may be addressed by the use of non-volatile solvents to force even less volatile substrates to undergo the cavitational activation. In recent times, the use of non-aqueous room temperature ionic liquids (ILs) as 'green' solvents in organic synthetic processes has gained considerable importance due to their negligible vapour pressure, solvating ability and easy recyclability.[3]

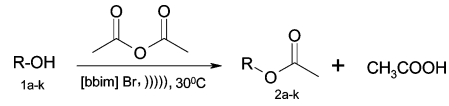
These ionic liquids have no vapour pressure, which should change considerably the characteristics of cavitation in the bulk. Indeed, we have recently shown that sonochemistry in ILs is a versatile tool to promote important organic transformations at ambient conditions with enhanced reaction rates. We have succeeded in promoting Heck and Suzuki reactions at ambient conditions without the need for a phosphine ligand under ultrasonic irradiation.[4,5] Ultrasound promoted nitration of phenols in the ionic liquid, ethylammonium nitrate, exhibiting significant enhancement in rates of reaction as well as high *para* selectivity.[6]

Continuing our investigations in this area, we report for the first time the ultrasound promoted *O*-acetylation of alcohols in the imidazolium based room temperature ionic liquids under ambient conditions in excellent isolated yields in short reaction times in the absence of any added catalyst.

The acetylation of alcohols is one of the most frequently and extensively used transformations in organic synthesis as well as in carbohydrate chemistry as it provides an efficient and inexpensive means for protecting hydroxyl groups in a multi-step synthetic process.[7] The standard *O*-acetylation reaction uses acetic anhydride as the primary reagent and a wide range of solvents and catalysts. A variety of catalysts ranging from bases such as 4-(dimethylamino) pyridine (DMAP),[8] Lewis acids such as $ZnCl_2$,[9] zeolites such as H-beta,[10] and enzymes such as lipases have been reported.[11] More recently, metal triflates in ionic liquids have been reported to be effective catalysts for the acetylation with acetic anhydride.[12] Although the catalysts are very useful, some of them suffer from a number of drawbacks. Metal triflates are expensive. Others are air and moisture sensitive and are frequently used for the acylation in environmentally harmful volatile organic solvents such as dichloromethane. The sonochemical methodology reported in this communication circumvents all the above mentioned drawbacks since the non-volatile IL can be efficiently recovered and reused and the process does not require any additional catalyst since the IL itself promotes the reaction.

Results and discussion

A variety of alcohols including aryl alkanols, alkanols, cinnamyl alcohol, menthol, and carbohydrates were subjected to the *O*-acetylation with acetic anhydride in the IL 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) as the solvent at ambient temperature (30 °C) under ultrasonic irradiation (Scheme 1).



Scheme 1

The reactions were monitored by TLC and taken to completion. The same reactions were performed under stirring without ultrasound (silent reactions) maintaining similar conditions. The time taken for complete conversion and the isolated

Green Context

The combination of ultrasound and ionic liquids provides a fast and simple route for the acetylation of alcohols without catalyst. In this work, a range of alcohols are smoothly acetylated using only ionic liquid solvent and ultrasound to provide the driving force. The products can often be distilled directly from the solution. Correlation of activity with the chemical shift of the 2-H of the solvent indicates that some acid catalysis from the ionic liquid can contribute too.

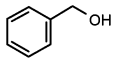
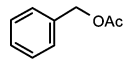
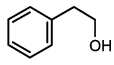
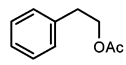
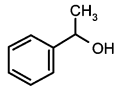
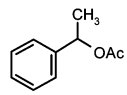
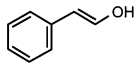
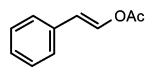
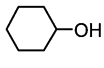
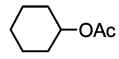
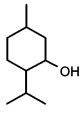
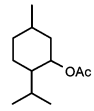
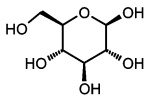
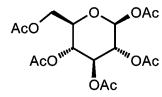
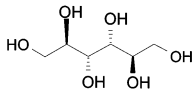
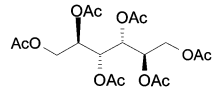
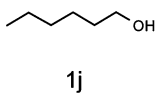
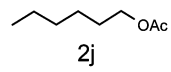
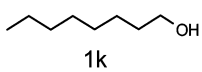
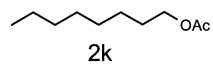
DJM

yields are recorded in Table 1. All the isolated products are known compounds reported in the literature. They were well characterized by their physical constants such as boiling points, melting points and additionally optical rotation for the chiral compounds. Their IR, ^{1}H-NMR, mass spectral and elemental analyses conformed with their structures.

All the reactions proceed to completion in just 5 to 30 min under ambient temperature except for 1-hexanol and 1-octanol for which 60 min of sonication was necessary under the same conditions. The respective esters were isolated in high purity and excellent yields (Table 1). Importantly, most of the esters, which are liquids, were isolated by a simple process of fractional distillation under reduced pressure leaving behind the ionic liquid. The solid esters *viz.*, the carbohydrate esters (entries 7 and 8) were selectively extracted into 20% petroleum ether (bp 60–80 °C) in ethyl acetate leaving behind the IL as an immiscible layer. The separation of the organic layer and removal of the solvent under reduced pressure furnished the pure esters. The recovery of the IL in each case was 98%. The IL, thus recovered, could be reused at least four times in the *O*-acetylation of benzyl alcohol without loss of activity.

The role of ultrasound in promoting the *O*-acetylation is evident from the fact that the corresponding reactions under stirred conditions without ultrasound (silent reactions) needed much longer time for complete conversion, in many cases in lowered yields (Table 1). Likewise, the unique role of ionic liquids in promoting the sonochemical reaction was evident from the fact that the *O*-acetylation of benzyl alcohol with acetic anhydride in molecular solvents such as dichloromethane, acetonitrile, chloroform, toluene and hexane under ultrasonic

Table 1 *O*-acetylation of alcohols under sonication and silent conditions

Entry	Alcohol (**1a–k**)	Time for complete conversion/min		Product (**2a–k**)	Yield (%)[a]		Physical constants
		Under sonication	Silent		Under sonication	Silent	
1	 1a	5	60	 2a	95	91	Bp 132 °C at 102 mmHg[13]
2	 1b	5	60	 2b	94	93	Bp 104 °C at 20 mmHg[14]
3	 1c	5	55	 2c	92	90	Bp 94 °C at 12 mmHg[14]
4	 1d	5	20	 2d	93	90	Bp 263 °C at 760 mmHg[15]
5	 1e	10	60	 2e	95	80	Bp 170 °C at 760 mmHg[15]
6	 1f	30	180	 2f	90	50	Bp 116 °C at 25 mmHg[16]
7	 1g	10	120	 2g	91	74	Mp 131 °C[17] $[\alpha]_D$ = +5.33° (c = 5 in $CHCl_3$)
8	 1h	30	120	 2h	80	72	Mp 123 °C[18] $[\alpha]_D$ = +25° (c = 5 in $CHCl_3$)
9	 1i	30	180	 2i	95	90	Bp 187 °C at 760 mmHg[19]
10	 1j	65	600	 2j	65	61	Bp 168 °C at 1 mmHg[15]
11	 1k	60	600	 2k	62	59	Bp 43 °C at 0.3 mmHg[20]

[a] Isolated yields.

irradiation did not show any conversion even after several hours of sonication.

Significantly, it was observed that the sonochemical acetylation of the carbohydrates *viz.*, D-(+)-glucose and D-(+)-mannitol gave the corresponding esters *viz.*, 1,2,3,4,6-pentaacetyl-*β*-D-glucose and D-(+)-mannitol hexaacetate, respectively, stereospecifically with retention of configuration. This was indicated by comparing their melting points and optical rotation with values reported in the literature (Table 1).

The sonochemical acetylation of benzyl alcohol was carried out in non-imidazolium ILs such as ethylammonium nitrate and 1-*n*-butyl-pyridinium tetrafluoroborate respectively. In both cases, the reaction did not proceed beyond 50% conversion even after several hours of sonication. This highlights the role of the imidazolium IL used in the present work which by virtue of its inherent Lewis/Brønsted acidities of the imidazolium ring protons promoted the reaction to complete conversion. Previous investigations by the same author[21] and study involving multinuclear NMR spectroscopy and conductivity measurements for the imidazolium ions correlating their acidity characteristics,[22–24] support the above observations.

The efficacy of the ILs to promote these sonochemical acetylation reactions was correlated to the nature of the anions. It was assumed that the nature of the anion will govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidities of the ILs. Thus the sonochemical acetylation of benzyl alcohol was performed in different 1,3-di-*n*-butyl imidazolium ILs, [bbim]X, with varying anions. The results are recorded in Table 2. The time for the complete

Table 2 *O*-acetylation of benzyl alcohol (**1a**) to benzyl acetate (**2a**) in various ionic liquids under sonication

Entry	Ionic liquid	(*) [a]	Time for complete conversion/min	Yield (%)[b]
1	[bbim]Cl	10.6	5	90
2	[bbim]Br	10.3	5	95
3	[bbim]ClO_4	9.02	15	89
4	[bbim]BF_4	8.87	25	90
5	[bbim]PF_6	8.86	30	91

[a] Chemical shift, δ-value, of H_a proton in ppm. [b] Isolated yields.

conversion was then correlated to the most deshielded imidazolium proton (H_a) chemical shifts (Table 2), indicative of the Lewis/Brønsted acidities of the different ILs. It was observed that the reaction becomes progressively faster with increasing Lewis/Brønsted acidity of the ILs as indicated by the increasing downfield shift of the imidazolium proton H_a.

In all probability, the hydrogen bond (Lewis/Brønsted acid) interaction of the most acidic hydrogen, H_a, of the imidazolium cation with the oxygen of the acetic anhydride as shown in Fig. 1 facilitates the generation of an acetyl cation required for the reaction. The influence of the acidity of this H_a proton for promoting the reaction was unequivocally established by conducting the sonochemical acetylation of benzyl alcohol in the ILs 1-*n*-butyl-2,3-dimethylimidazolium tetrafluoroborate, ([bdmim]BF_4) and 1,3-di-*n*-butyl-2-methylimidazolium bromide ([bbmim]Br), respectively. The conversions do not go beyond 50 and 54%, respectively, even after 5 h of sonication.

Conclusion

The *O*-acetylation of alcohols with acetic anhydride to the corresponding esters has been achieved in short reaction times

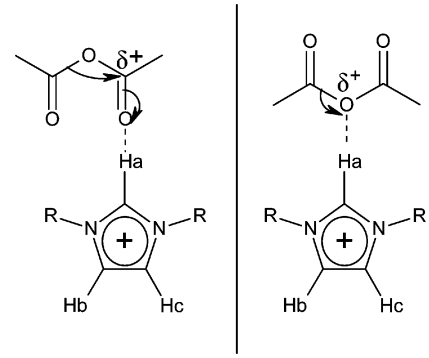


Fig. 1 The H_a (most acidic) hydrogen bond interaction of the imidazolium cation with oxygen of acetic anhydride.

with excellent isolated yields under ambient conditions without the need for any additional catalyst by the combined use of ultrasonic irradiation and a 'green' room temperature ionic liquid as a reaction medium and promoter. The esters could be easily isolated from the reaction mixture either by fractional distillation or selective extraction leaving behind the non-volatile IL pure enough for reuse in several recycles. Thus this method offers an improved practical alternative to conventional acid/base catalysed thermal processes and is environment friendly with minimal waste. Further investigations to broaden the scope of this technology are in progress.

Experimental

General

All chemicals were of research grade and were used as obtained from Aldrich or Fluka. The reactions were carried out in a thermostated (30 ± 1 °C) ultrasonic cleaning bath (Branson 5200 E4) at 50 kHz. The ultrasonic cleaner had an output power of 120 W and a power supply of 450 W. The tank dimensions were 290 × 240 × 150 mm with a liquid holding capacity of 9.5 l. The reactions were carried out in a round-bottomed flask of 25 ml capacity suspended at the center of the cleaning bath, 5 cm below the surface of the liquid.

The melting points are uncorrected. IR spectra were recorded on a Mattson Research Series FT-IR spectrometer, mass spectra on a Finnigan Mat-1020 automated GC/MS spectrometer and ^{1}H-NMR spectra on a Bruker-200 MHz spectrometer. The boiling points and the melting points are compared with the reported literature values.

Preparation of different ionic liquids

The ILs [bbim]Br and [bbim]BF_4 were prepared as per the methods reported by us.[4,5] The IL [bbim]Cl was prepared using *n*-butyl chloride as an alkylating agent in a manner similar to the method described for [bbim]Br. The ILs [bbim]PF_6 and [bbim]ClO_4 were prepared by metathesis of [bbim]Br using the corresponding acid of the anion, exactly as per the method reported by us for [bbim]BF_4. The IL [bdmim]BF_4 was procured from ACROS Organics and used as such.

1-Butyl-2-methylimidazole

2-Methylimidazole (10 g, 122 mmol) and KOH (7.5 g, 134 mmol) in 25 ml of acetonitrile was stirred for 1 h. *n*-Butyl bromide (16 g, 122 mmol) was added drop wise to the above mixture over 45 min maintaining the temperature of the reaction

mixture by external cooling at 10–15 °C. The resulting mixture was further stirred for 3 h at 30 °C. The reaction mixture was filtered to remove KBr and the solvent was distilled off under reduced pressure to leave behind a pale brown liquid. This was further subjected to distillation under reduced pressure (170 °C/5 mm) to yield pure product (13.25 g, 79%). IR (Neat): 3369, 2960, 2933, 2874, 1667, 1618, 1525, 1499, 1465, 1425, 1364, 1276, 1219, 1144, 1099, 1072, 985, 949, 918, 753, 729 cm^{-1}. ^{1}H-NMR (300 MHz): (d, ppm) 0.89(t, J = 7.32, 3H), 1.30(m, 2H), 1.65(m, 2H), 2.31(s, 3H), 3.76(t, J = 7.32, 2H), 6.75(s, 1H), 6.84(s, 1H). Anal. Calc. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.42; H, 10.30; N, 20.35%.

1,3-Di-*n*-butyl-2-methylimidazolium bromide

A mixture of 1-butyl-2-methylimidazole (12 g, 87 mmol) and *n*-butyl bromide (12.5 g, 91 mmol) was heated at 100 °C for 6 h and the reaction was followed by TLC using 2% methanol in ethyl acetate as eluent. After completion of the reaction, excess *n*-butyl bromide was removed at 80 °C under reduced pressure (10 mmHg) to afford the required ionic liquid (21.8 g, 95.4%), which was fully characterized. IR (Neat): 3662, 3393, 3173, 3062, 3018, 2961, 2934, 2876, 2453, 1667, 1619, 1583, 1530, 1465, 1383, 1336, 1296, 1245, 1216, 1197, 1136, 1116, 1083, 947, 925, 881, 751 cm^{-1}. ^{1}H-NMR (300 MHz): (δ, ppm) 0.89(t, J = 7.32, 6H), 1.32(m, 4H), 1.75(m, 4H), 2.76(s, 3H), 4.23(t, J = 7.32, 4H), 7.59(s, 1H). Anal. Calc. for $C_{12}H_{23}N_2Br$: C, 52.36; H, 8.36; N, 1018. Found: C, 52.15; H, 8.64; N, 10.33%.

General procedure for the sonochemical acetylation

A mixture of alcohol (10 mmol) and acetic anhydride (11.1 mmol) in 1,3-di-*n*-butyl imidazolium bromide ([bbim]Br, 2.0 g) was sonicated in an atmosphere of argon at ambient conditions in a thermostated (30 ± 1 °C) ultrasonic cleaning bath. The reactions were monitored by TLC and taken to completion. The same reactions were performed under stirring without ultrasound (silent reactions) maintaining similar conditions. After the complete conversion, all the esters except those of carbohydrates (Table 1, entries 7 and 8), which are liquids, were isolated by subjecting the reaction mixture to fractional distillation under reduced pressure leaving behind the non-volatile IL. After the recovery of acetic acid as the first fraction, esters were distilled out at their respective boiling points as indicated in Table 1. Alternatively, the solid esters (Table 1, entries 7 and 8) were completely and selectively extracted into 20% petroleum ether (bp 60–80 °C) in ethyl acetate (2 × 25 ml) leaving behind the IL as an immiscible layer. The separation of the organic layer and removal of the solvent under reduced pressure furnished the pure esters. In both the cases the recovered IL was pure enough for use in several recycles.

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Utilization of adsorption effects for the continuous reduction of NADP+ with molecular hydrogen by *Pyrococcus furiosus* hydrogenase

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The use of hydrogenases for the direct reduction of cofactors with molecular hydrogen provides a means to utilize this clean and strong reducing agent for use in reductive biotransformations. The hydrogenase I from *Pyrococcus furiosus* is a promising enzyme for the production of NADPH from NADP+ with molecular hydrogen. We observed adsorption of the active enzyme by using cyclic voltammetry. Our investigations revealed an electroactive enzyme species adsorbed onto the surface of the working electrode. This facile route for immobilisation of the active enzyme was subsequently utilized for the continuous reduction of NADP+ to NADPH with molecular hydrogen in a continuously operated fluidized bed reactor with hydrogenase adsorbed on graphite beads. The reactor was operated at low conversion for more than 40 residence times (80 h). The apparent retention was found to be 98% on unmodified graphite carriers.

Introduction

Hydrogenases are enzymes capable of activating dihydrogen. They are found in numerous microorganisms. In the habitats of hyperthermophilic microorganisms where hydrogen is abundant, hydrogenases play an important role in hydrogen metabolism. The majority of these enzymes contain different metal clusters,[1] which are responsible for the redox capabilities.

The hydrogenase I from the hyperthermophilic archaeon *Pyrococcus furious* (*Pf* hydrogenase)[2] (EC 1.18.1.99) shows interesting redox properties, particularly the activation of molecular hydrogen. It is capable of catalyzing the direct reduction of NADP+ to NADPH with molecular hydrogen.[3,4] Although the exact physiological role in the archeon is still unknown,[5] the enzyme shows *in vitro* activity towards the activation of dihydrogen, and has been utilized in biotransformations for dihydrogen production and reduction of dyes.[3,4,6]

We are interested in the *Pf* hydrogenase especially in its ability to reduce pyridine nucleotides and for utilization in biotransformations by means of cofactor regeneration.[7–10] For this purpose it is necessary to investigate the catalytic synthesis of the reduced cofactor as the first step of the reaction.[11] Utilization of hydrogen for reduction of NADP+:

$$NADP^+ + H_2 \rightarrow NADPH + H^+$$

would provide a cheap and clean source for the generation and regeneration of the reduced phosphorylated nicotinamide cofactor.

Electrochemistry has proven to be a powerful technique for the investigation of these redox active enzymes. Electrochemical investigation of *Pf* hydrogenase has also been carried out in combination with other analytical techniques[12] and along with other metalloproteins of *Pf*.[13,14] Hydrogenases from other sources have been investigated electrochemically with respect to their redox or electrochemical properties[15] (*Alcaligenes eutrophus*,[16] *Thiocapsa roseopersiciana*,[17] *Thermococcus celer*,[18] *Desulfovibro vulgaris*,[19] *Chromatium vinosum*,[20] and *Megaspherae elsdinii*[21]).

Furthermore, the direct electrochemistry of immobilized enzymes has been demonstrated to provide means for the electrochemical generation and regeneration of NADH. This has been performed with isolated hydrogenase from *Alcaligenes eutrophus* by preparation of catalytic films,[22] and electrodes modified with whole cells of *Desulfovibro gigas*.[23] To yield an immobilized electroactive catalyst on the surface of the electrode, these approaches require the binding of the catalytically active species by laborious methods. Lately adsorption of the subcomplex Iα of mitochondrial NADH:ubiquinone oxidoreductase was demonstrated.[24]

We carried out cyclic voltammetric experiments to reveal whether the *Pf* hydrogenase shows adhesive properties. By means of cyclic voltammetry adsorption can be detected, since the observation of "line-crossing" phenomena can be ascribed to adsorption of electroactive species on the electrode surface.[25]

Methods and material

All chemicals were of the best available quality and obtained from Sigma (Steinheim, Germany), if not stated otherwise.

Green Context

NADPH is a potentially very useful reductant which is formed by reduction of NADP+. This paper demonstrates the utility of an enzyme to carry out this reduction, in a continuous manner, using molecular hydrogen. The enzyme is readily adsorbed onto an electrode where it is active in the reduction of NADP+. This observation has potential in a number of applications. ***DJM***

$NADP^+$ (sodium salt) was obtained from Jülich Fine Chemicals, (Jülich, Germany). Deionized water was obtained by means of nanofiltration (Milli-Q académic, Millipore, Eschborn, Germany). Gases of 99.9990% purity were obtained from Messer (Krefeld, Germany). All buffers were degassed with helium and handled under an inert atmosphere of argon or nitrogen by standard Schlenk techniques. Protein content was determined by the method described by Sedmark *et al.*[31]

Concentrations of $NADP^+$ and NADPH were determined by capillary electrophoresis,[30] with uridine as the internal standard after dilution if appropriate. Standard conditions were: 40 mM potassium phosphate, 10 mM borate buffer, pH = 8.5, 30 kV, 40 °C, capillary: uncoated silica (50 cm total length, 43 cm to detection window, 50 μm inner diameter), typical migration times: uridine 2.9 min, $NADP^+$ 7.1 min, NADPH 9.9 min.

The enzyme preparation was derived following the procedure described by Haaker *et.al.*[3] The cell free extract was purified in one chromatographic step and the resulting crude enzyme preparation was concentrated *via* ultrafiltration to a protein content of 58 mg mL^{-1}. The enzyme preparation was used without further purification.

The cyclic voltammetric experiments were performed on a BAS 100 B/W Version 2.3 Electrochemical Workstation (Bioanalytical Systems, West Lafayette, Indiana, USA) using an airtight thermostated three-electrode electrochemical cell. The working electrode was a glassy carbon disk (3 mm diameter), while the counter electrode was a platinum wire. All potentials were measured and quoted *vs.* Ag|AgCl|3 M KCl (+0.21V *vs.* SHE) as the reference electrode. Before the addition of enzyme, the working electrode was polished mechanically to a mirror finish using 0.5 μm alumina powder and then rinsed with deionized water. The experiments were performed using a solution of 340 μg *Pf* hydrogenase preparation in 2 mL of 100 mM potassium phosphate buffer, pH = 8. The experiments were firstly carried out under an atmosphere of nitrogen (80 °C), which was subsequently replaced by hydrogen. During the experimental series the temperature was kept constant and the sweep rate varied from 8 to 100 mV s^{-1}.

The continuously operated fluidized bed reactor was adapted from a setup described by Biselli *et al.*[29] for cell culture, and slightly modified for use under oxygen-free conditions. The flow sheet is shown in Fig. 1. The total volume of the reactor

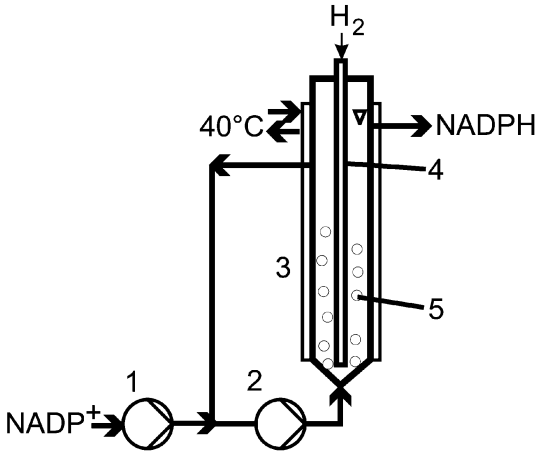

Fig. 1 Flow sheet of reactor setup: (1) dosing pump, (2) circulation pump, (3) glass cone with thermostating jacket, (4) tubular PTFE membrane, (5) graphite or glass beads.

was 25 mL. Hydrogen was supplied *via* a non-porous (dense) tubular PTFE membrane (**4**) (OD = 3.1 mm, ID = 2.2 mm) of 10 cm length in the center of the fluidized bed. The fluidized bed reactor (**3**) was constructed of glass. All connections and tubings were made of steel using viton sealings. A magnetic coupled gear pump (**2**) (Verder, Austria) was used to establish circulation, and a P-500 piston pump (**1**) (Amersham Pharmacia Biotech, Freiburg, Germany) equipped with a mass flow metering system (not shown) (Bronkhorst, Ruurlo, Netherlands) acted as a dosing pump as described previously.[32] The reactor was thermostated to 40 °C. The beads (**5**) were either graphite (Sigradur®, SGL Carbon, Bonn, Germany, 0.4–0.6 mm in diameter and used without further purification) or glass (unmodified porous SIRAN®, Schott, Germany, 0.7–1.0 mm in diameter, which was achieved by sieving as described previously[29]). The reactor was flushed with 10 volumes (250 mL) of degassed and deionized water prior to use. Subsequently, the feed was changed to 12 mM $NADP^+$ in 100 mM potassium phosphate buffer (pH = 8) for 5 volumes (125 mL) at a flow rate of 12.5 mL h^{-1}. The central tubular PTFE membrane was flushed with hydrogen; and pressurized to a inner pressure of 4 bar during the experiment. The outflow was collected in fractions and analyzed for yield and conversion by means of capillary electrophoresis, and for protein content.

The experiments were started by adding 0.42 mL of the hydrogenase preparation (protein content 58 mg mL^{-1}), equivalent to 1.0 mg mL^{-1} protein content in the reactor. Prior to the addition the hydrogenase was activated following the published procedure protocol[3] by exposure to a hydrogen atmosphere at 80 °C. During the experiment the flow rate of the dosing pump was kept constant at 12.5 mL h^{-1}, resulting in a residence time of τ = 2 h. The flow rate in the circulation loop was adjusted to a level where no beads were driven out of the fluidized bed (1–2 L min^{-1}).

Results and discussion

The cyclic voltammetric investigations were carried out to reveal if the absorbed *Pf* hydrogenase absorbed onto surfaces is electrochemically active. Cyclic voltammetric experiments were performed first under an atmosphere of nitrogen, which was then replaced by hydrogen. An airtight cell was used with a standard three electrode setup, in which oxygen free conditions could be maintained. After introduction of hydrogen, the cyclic voltammetric experiments of the enzyme preparation of *Pf* hydrogenase showed a line-crossing phenomenon in the presence of hydrogen as depicted in Fig. 2. This line form is evidence for adsorption of an electrochemically active species.[25,26]

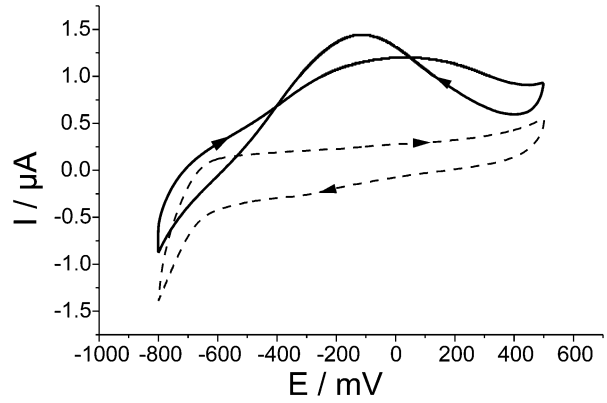

Fig. 2 Cyclic voltammograms of hydrogenase under nitrogen atmosphere (dashed line) and in the presence of hydrogen (solid line), sweep direction is indicated (80 °C, 8 mV s^{-1}, glassy carbon, *vs.* Ag|AgCl, other conditions see text, anodic current has positive sign).

We assign the adsorbed species to the $NADP^+$ reducing activity, as selective immobilization during the continuous experiments was observed (see below). It can then be deduced that hydrogenase is adsorbed and probably capable of direct electron transfer. The adsorption might be considered as

electrodeposition of a metalloprotein following the activation with hydrogen.

Further evidence for adsorption can be taken from the observation that the peak current of the backward scan increased, when the sweep rate is decreased (Fig. 3). The peak

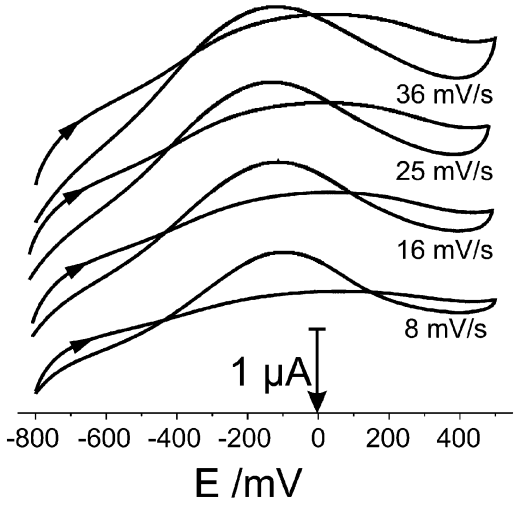

Fig. 3 Cyclic voltammograms (superimposed) of hydrogenase in the presence of hydrogen at different velocities (80 °C, 8–36 mV s^{-1}, glassy carbon, *vs.* Ag|AgCl, other conditions see text, anodic current has positive sign), forward sweep direction is indicated.

current corresponds to the amount of electroactive species deposited during the forward sweep due to the reaction with hydrogen. Hydrogen could be eliminated as the cause for the line-crossing by independent experiments, and by changing the sweep direction which essentially gave the same results (data not shown).

Activation of the enzyme is most probably due to reduction by hydrogen at 80 °C[14,33] to form an electrochemically active enzyme species. A possible explanation might be a reorganization or reconstitution of the enzyme subunits as reported for other hydrogenases (*e.g. Alcaligenes eutrophus* H16,[34] *Rhodococcus opacus*[35]). An altered structure might also lead to the exposure of a hydrophobic surface on the enzyme, which would be a possible explanation for adsorption.

However, only the adsorption of an electrochemically active species on the surface of the electrode can be deduced from the cyclic voltammetric experiments alone, since the hydrogenase might not be the only electroactive species in the preparation used in investigations.[3]

Motivated by the observation of the adhesive properties of the enzyme preparation, attempts were made to utilize them for immobilization of the active enzyme. A setup was used with a fluidized bed where hydrogen was supplied *via* a dense PTFE (polytetrafluoroethylene) membrane (Fig. 1). The setup was chosen because conversion is directly correlated with enzyme activity in a continuously operated stirred tank reactor (CSTR). Therefore the input concentration of $NADP^+$ was set to 12 mM to operate the reactor in a region where the linear correlation of enzymatic activity holds true. This is opposed to operating at lower concentration with higher conversion where the amount of enzyme is not the limiting parameter. Thus conversion can be linearly correlated to the retention and stability of the enzyme. In order to synthesize under these conditions the unstable NADPH intermediate, a flow scheme closer to plug flow conditions would be superior, but then enzyme activity would not be correlated with conversion. The fluidized bed reactor was preferred to a fixed bed reactor for better mass transport of dissolved hydrogen, avoiding concentration gradients over the cross-section of the bed.[27–29]

Immobilization experiments were carried out with beads of graphite or glass. With graphite beads the reactor could be operated for more than 80 h (number of residence times more than 40) at a low conversion level, ensuring linear correlation of conversion and activity. A retention of 98% was obtained; whereas the retention on glass carriers was found to be too low for technical application. The decreased affinity to glass beads is probably due to surface specific adsorption. Overload of the immobilization matrix would lead to another curve form which cannot be described as exponential decay. Conversion and the relative protein content as a function of the number of residence times (time τ) for graphite beads as the immobilization matrix are shown in Figs 4 and 5 respectively. In Fig. 6 the conversion

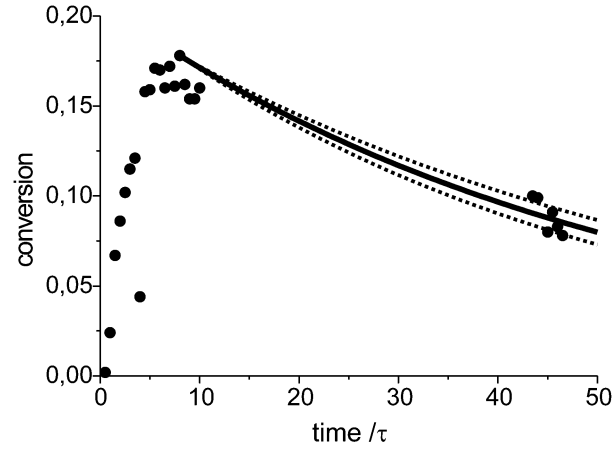

Fig. 4 Conversion of reactor outflow as a function of the number of residence times with immobilization on graphite beads. The straight line gives a relative retention value of 0.981, dotted lines represent the standard deviation of ±0.002. (τ = 2 h, 40 °C, pH = 8, [*Pf* hydrogenase]0 = 1 mg mL^{-1}, Inlet [$NADP^+$] = 12 mM).

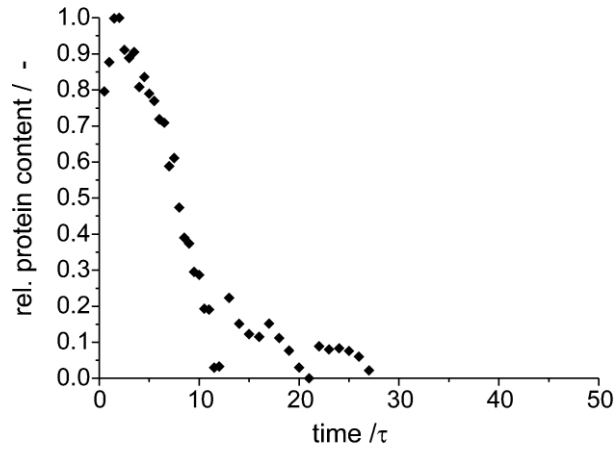

Fig. 5 Relative protein content of reactor outflow as function of the number of residence times. After t/τ = 30 protein content was below the detection limit (τ = 2 h, 40 °C, pH = 8, [*Pf* hydrogenase]0 = 1 mg mL^{-1}, Inlet [$NADP^+$] = 12 mM).

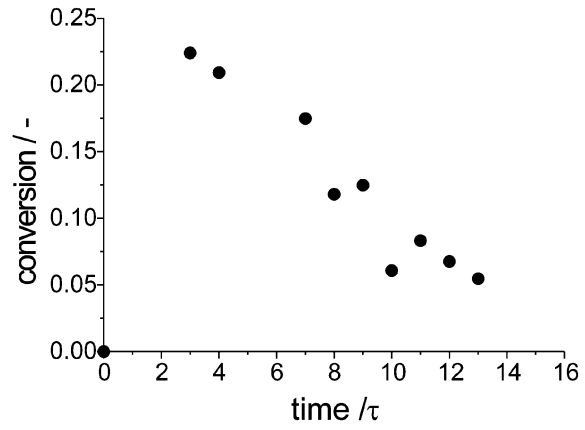

Fig. 6 Conversion of reactor outflow as a function of the number of residence times with immobilization on glass beads (τ = 2 h, 40 °C, pH = 8, [*Pf* hydrogenase]0 = 1 mg mL^{-1}, Inlet [$NADP^+$] = 12 mM).

for the immobilization on glass beads is shown. Generally, the obtained yield is lower than the conversion (data not shown) due to instability of NADPH under the reaction conditions.[36] It is noteworthy that the maximum conversion level is equal to a NADPH concentration of about 2 mM in both cases. So, presumably, operating at lower inlet concentrations of $NADP^+$ would have given higher conversion levels. However, the drastic loss of activity, as observed in the case of the glass beads, would not have been observable, because enzyme activity would not have been limiting. The decrease in conversion for the graphite beads can be described by exponential decay, with a retention value of $r = 0.981 \pm 0.002$, as depicted in Fig. 4. However, it should be noted that this description is weak due to a lack of measurements. This is mirrored by the relative large confidence bands. The protein content in the outflow of the reactor does not correlate with the remaining activity in the reactor. Consequently the $NADP^+$ reducing species is bound to the surface. Also the apparent loss of activity of 2% per residence time (1% per hour) is in the order of magnitude of deactivation for the hydrogenase (data not shown). It is therefore plausible, that the true retention value due to adsorption is greater. For conditions optimized for enzyme stability, longer run times are possible.[4]

Conclusions

By conformation of the adsorption of hydrogenase activity by immobilization and continuous application in a fluidized bed, the adsorbed electrochemical active species can be correlated with hydrogenase activity. Adsorption onto surfaces provides a method for the immobilization of the active enzyme. However, the adsorption as a tool for immobilization has to be investigated further. It may provide means for applications in bio fuel cells without the need of an additional immobilization matrix, since the cyclic voltammetric experiments show that the adsorbed species is electroactive. Thus further experiments have to be conducted to reveal whether the adsorption might be considered as electrodeposition.

The operating stability of the hydrogenase was demonstrated by the continuous application. Furthermore, the results show that hydrogenase I from *Pyrococcus furiosus* can be used for the continuous synthesis of NADPH by reduction of $NADP^+$ by molecular hydrogen. Therefore the reactor has to be optimized for yield in a true attempt for the synthesis of NADPH. Also other modes of recycling for the promising enzymatic catalyst are the subject of current research.[4]

Acknowledgements

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Selective solid-state brominations of anilines and phenols

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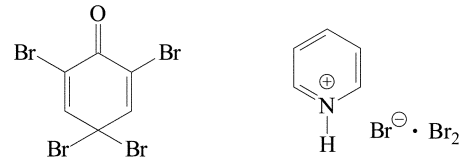
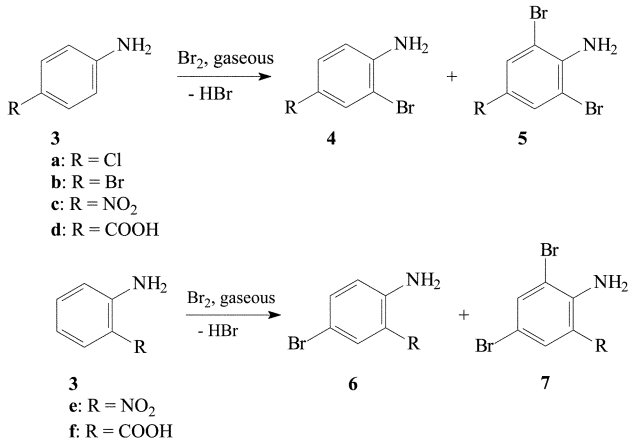
Novel environmentally benign solid-state brominations of anilines and phenols with gaseous bromine and solid bromination reagents are described. In most cases the reactions proceeded in the absence of solvents with higher yields and selectivities than in solution.

Organic solid-state reactions are very promising alternatives to reactions in solution if they are more selective and efficient or yield sensitive products which are complicated or even impossible to obtain in solution.[1,2] It has long been recognized that brominations can be carried out in the solid state with gaseous bromine,[3–9] and recently with NBS[10,11] or ammonium tribromides.[12] Often the yields are higher than that in comparable solution reactions, but selectivities are nearly the same. We report now on preparatively useful solid–solid aromatic brominations of anilines and phenols with gaseous bromine, 2,4,4,6-tetrabromo-cyclohexa-2,5-dienone **1**, and pyridinium hydrobromide perbromide **2**.



1 **2**

The direct bromination of anilines with bromine in solution often results in polybromination and requires protection of the amino function, for example as acetanilide. But in gas–solid reactions gaseous bromine reacts with solid anilines **3**, mostly with excellent yields, giving the products shown in Scheme 1. If



3
a: R = Cl
b: R = Br
c: R = NO_2
d: R = COOH

4 **5**

3
e: R = NO_2
f: R = COOH

6 **7**

Scheme 1 Gas–solid brominations of crystalline anilines with bromine.

necessary one recrystallization from ethanol/water is enough to purify the products. In comparison to the results obtained by carrying out the reaction in solution (the solvent is, in most cases, acetic acid), the reaction in solid-state proceeds more effectively under much milder conditions (Table 1). The

Table 1 Gas–solid brominations of anilines with bromine

Aniline	Brominated products: conversion in %[a]	Isolated product: yield in %	Product in solution: yield in %
3a	**4a**: 27	**5a**: 68	**5a**: not given [13]
	5a: 73		
3b	**4b**: 25	**5b**: 63	**5b**: not given [14]
	5b: 75		
3c	**4c**: 16	**5c**: 65	**5c**: 98 [15]
	5c: 81		
	3c: 3		
3d	**5d**: 100		**5d**: 82 [16]
3e	**6e**: 83	**6e**: 69	**6e**: 60 [17]
	7e: 14		**7e**: 14 [17]
	3e: 3		(+ 26% *o*-bromination [17])
3f	**6f**: 100		**6f**: 87 [18]

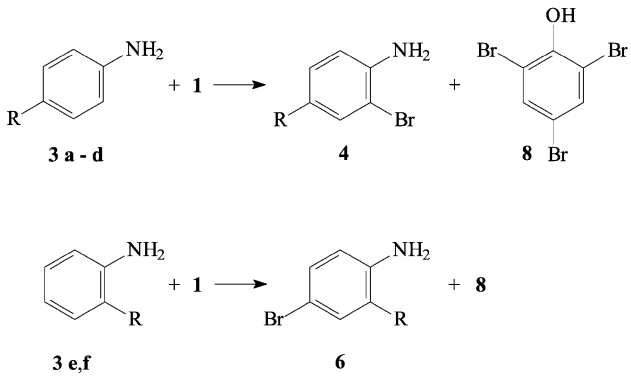
[a] Determined by ^{1}H NMR.

selectivities are similar to reactions in solution but the yields are higher and in cases of aminobenzoic acids **3d** and **3f** even quantitative. The yields are likewise remarkably higher than for solid–solid brominations with NBS. For example, cogrinding of **3a** with NBS results in formation of the 2,6-bromo derivative in only 45% yield.[11]

The gas–solid reactions were carried out by placing 10 mmol **3** in a desiccator with excess bromine gas. After 24 h the solid crude product was washed with 1 M NaOH or in the cases of **3d** and **3f** with methanol. If necessary the products were recrystallized from ethanol/water. Still higher yields and better selectivities were afforded by the solid–solid brominations of anilines with **1**, as shown in Scheme 2 and Table 2. This reaction always leads to selective monobrominations, preferentially in the *para* position but in the *ortho* position if the *para* position is

Green Context

Solvent free brominations are described, both using solid–solid reactions and solid–gas reactions, the latter using bromine directly. The selectivities and activities are often significantly better than in solution. Most of the solid bromination reagents can be readily regenerated with bromine *ex situ*. ***DJM***



Scheme 2 Solid–solid bromination of anilines with **1**.

Table 2 Solid-state bromination of anilines with **1**

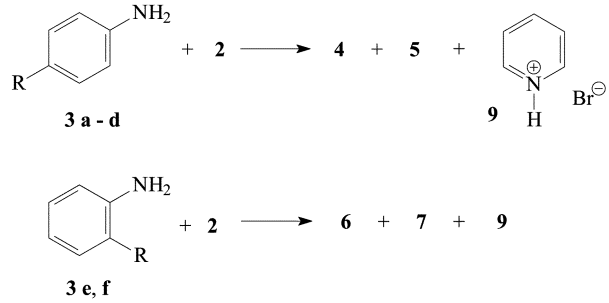
Aniline	Product: yield in %	Product in solution: yield in %
3a	**4a**: 87	
3b	**4b**: 88	
3c	no reaction	**4c**: 64 [19]
3d	no reaction	
3e	**6e**: 91	**6e**: 91 [20]
3f	**6f**: 87[a]	**6f**: 82 [20]

[a] Accelerated by ultrasound.

occupied, because the bulkiness of the bromination reagent **1** causes an additional selectivity. The same effect is found for comparable reactions in solution, where the yields are also in the same range.[19,20] For the reactions 1 mmol of each reactant were ground together in a mortar and the resulting powder was allowed to stand for 10 h under occasional grinding. **3f** must placed for 10 h in an ultrasound bath (23 kHz) for a complete reaction. Afterwards 2,4,6-tribromophenol **8** was washed away from the reaction mixture with 1 M NaOH or in the case of **3f** with toluene. **8** can be easily isolated from this filtrate and recycled to **1** by bromination with bromine in acetic acid.[20]

This kind of reaction can be comfortably monitored by measurement of the solid-state UV spectrum. For example, the UV spectrum of a 1 : 1 molar mixture of powdered **1** and **3b** shows a fast and efficient reaction. The powdered mixture was shaken for 1 min and kept at room temperature for 10 h. The UV spectrum was measured in the solid-state every 15 min for the first 2 h. The peaks of the orange **1** disappeared during the solid-state reaction and the new signal of 2,4-bromaniline at 297 nm formed (Fig. 1). This is the first example of monitoring a chemical solid-state reaction by solid-state UV, since only one example of the UV monitoring of an inclusion complexation has been reported so far.[21]

The solid-state bromination of anilines with **2** results in similar selectivities as the gas–solid brominations but the yields are lower (Scheme 3 and Table 3). These reactions were carried



Scheme 3 Solid–solid reaction of anilines with **2**.

Table 3 Solid–solid bromination of anilines with **2**

Aniline	Molar ratio **2** : **3**	Isolated product: yield in %
3a	2 : 1	**5a**: 56
3b	2 : 1	**5b**: 35
3c	1 : 1	**4c**: 62
3d	2 : 1	**5d**: 60[a]
3e	1 : 1	**6e**: 46
3f	2 : 1	**7f**: 48[a]

[a] accelarated by ultrasound

out by cogrinding 2 mmol of **2** (or in the cases of **3a**, **b**, **d**, and **f**: 4 mmol) and 2 mmol aniline in a mortar. After 24 h the crude product was washed with 1 M NaOH (**3a–c**, **e**) or water (**3d**, **f**) and recrystallized from ethanol. **3d** and **3f** were placed in an ultrasound bath for 10 h to achieve complete reaction.

As shown by Labes and Blakeslee, phenols can be brominated by gaseous bromine in the form of their sodium salts, but

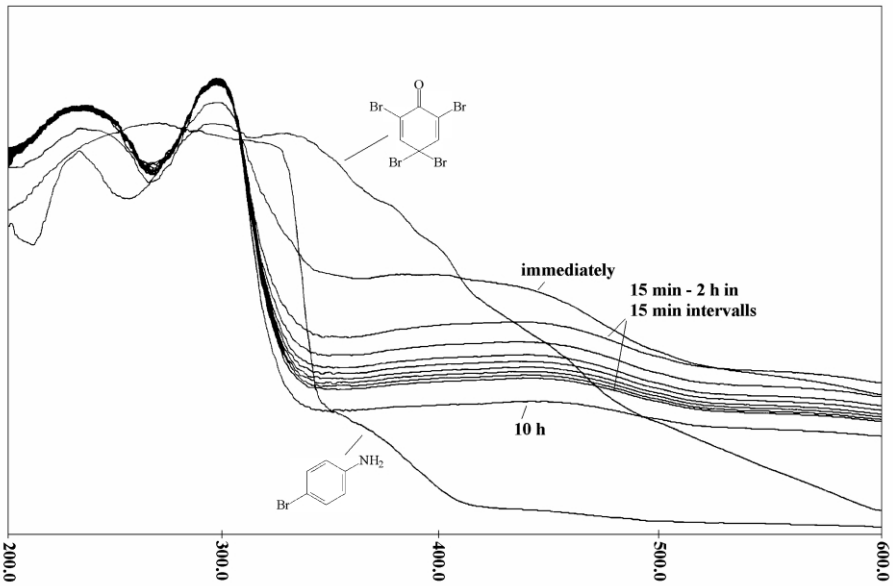
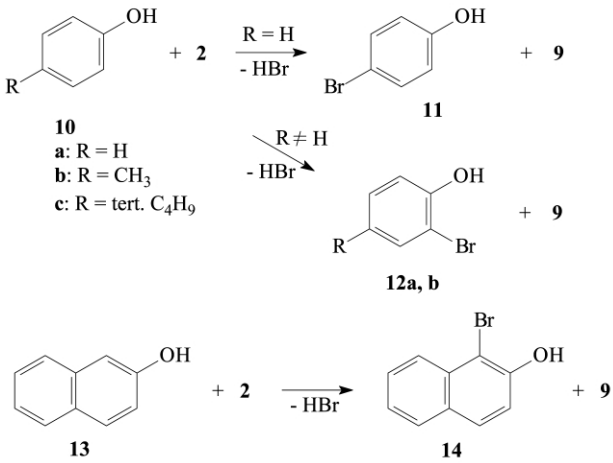


Fig. 1 Solid-state UV spectra measured every 15 min for the first 2 h to monitor the reaction of **1** with **3b**. The reaction was complete within 10 h.

the selectivities are in the same range as for reactions in solution.[5] On the other hand the solid–solid bromination of phenols with NBS gives only medium yields.[10] To increase yields and selectivities we developed a new solid–solid syntheses just by cogrinding phenols **10** with **2** (1 mmol of each) in a mortar (Scheme 4). Most reaction mixtures turned into



Scheme 4 Solid–solid reaction of phenols with **2**.

liquid after 5 min and released HBr gas. Two hours later the reactions are complete and the pyridinium hydrobromid **9** can be washed away with water, so that the pure product can be separated with excellent yields by filtration (Table 4). In the

Table 4 Solid-state brominations of phenols with **2**

Phenol	Product: yield in %	Product with Br_2 in solution: yield in %
10a	**11**: 89	**11**: 84 [22]
10b	**12a**: 88	**12a**: not given [23]
10c	**12b**: 95	**12b**: 97 [24]
13	**14**: 98	**14**: not given [25]

case of **11** the crude product must be distilled because 4-bromophenol will not crystallize in the presence of moisture. Again the bromination agent **2** can be recycled from **9** by reaction with bromine in acetic acid.[26]

In summary, we have found different methods for environmentally benign mono- and dibrominations of anilines in the solid-state, that can be more easily and safely executed than comparable reactions in solution. The greatest benefit of the solid-state reactions is the avoidance of solvents during the reaction phase. For highly selective monobrominations of anilines with excellent yields, **1** is the reagent of choice. With gaseous bromine, dibrominations with up to 100% yield under a complete renunciation of any solvents are possible. Phenols can be brominated best with **2**, which results in monobrominated products, again with very high yields. In these cases no waste producing purification steps are necessary since the products arise directly in the pure state after washing with alkali, methanol or toluene without use of energy. In conventional solution-phase brominations the freed HBr must be neutralized though. Even if the products must be recrystallied, the reaction solvents are saved.

Experimental

The solid-state UV techniques have been described in detail elsewhere.[21] Gas–solid bromination of anilines with bromine: 10 mmol **3** in a test tube and 20 mmol bromine in a second test tube were placed in a desiccator. The mixtures were left overnight at room temperature. After the reaction was complete, the slight excess of bromine and HBr was recovered in a cold trap at 77 K. The solid residue was washed with 1 M NaOH or MeOH. The products were recrystallized from ethanol/water. **5d** and **6f** need no workup. The structure of the products were proved by mp, IR, and NMR; the yield were calculated by the weight.

Solid-state bromination with **1** or **2**: equimolar amounts of crystalline anilines **3** or phenols **10** were ground together in a mortar with the bromination reagents **1** or **2** under the conditions stated in the relevant tables. After the reaction was complete, the solid product mixture was washed and if necessary recrystallized. The products were identified by comparison with known mps, IRs, and NMRs.

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Combined microwave and ultrasound accelerated Knoevenagel–Doebner reaction in aqueous media: a green route to 3-aryl acrylic acids

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The microwave and ultrasound combined aqueous Knoevenagel–Doebner reaction proves an efficient and eco-friendly route for preparing 3-aryl acrylic acids in good yields. This organic solvent-free protocol is valuable since rapid reaction rate, low energy consumption, waste minimization, simple operation and easier product work-up can be achieved.

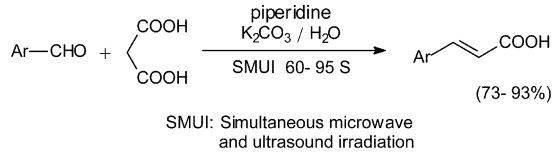
Introduction

Cinnamic acid and its derivatives are important reagents in organic synthesis both as intermediates and final products. Routinely, they were obtained from the reaction between aromatic aldehydes and malonic acid (Knoevenagel–Doebner reaction)[1] or acetic anhydride (Perkin reaction).[2] The classic Knoevenagel–Doebner reaction was carried out in organic solvents catalysed by secondary or primary amines.[3] However, organic solvents used in these transformations, *e.g.* pyridine, are high on the list of damaging chemicals because of their volatile nature, considerable toxicity and use in large quantities for the reaction. On the other hand, the secondary amines employed as catalysts in these procedures are difficult to recover and often entail severe environmental pollution during the process of waste disposal. Therefore, the introduction of new methods, inexpensive reagents and environmentally friendly conditions for such transformations is still in demand.

The "greening" of global chemical manufacturing by minimizing energy consumption and waste production has become a major concern for the chemical industry.[4] In the last decade, there has been incredible growth in research involving the use of water as a green, environmentally benign replacement for a wide range of processes that currently rely on conventional organic solvents, as the water is superior to many other organic solvents from both environmental and economical points of view.[5] More recently, Bigi and co-workers[6] have reported the uncatalysed Knoevenagel condensation between aromatic aldehydes and highly activated malononitrile in aqueous solution.

Previous work[7] of our group has demonstrated that simultaneous microwave and ultrasound irradiation (SMUI) gave significant rate enhancements and improved yields in heterogeneous organic reactions. Many reactions that typically need many hours to reach completion with conventional heating can be brought to full conversion in only seconds to minutes by utilizing this powerful tool.

In continuation of our ongoing efforts in this area, by using SMUI techniques, we have developed a very efficient synthetic method for the preparation of 3-aryl acrylic acids in aqueous media (Scheme 1). This method involves the use of eco-friendly solvent, and gives desired products in a short period with good to excellent yields.



Scheme 1

Results and discussion

In this method, combined microwave and ultrasound irradiation play an important role in significantly enhancing the reaction rate as well as avoiding the use of toxic or flammable organic solvents, for example, pyridine or ethanol. This reaction is of a wide scope, and applies to aromatic aldehydes bearing various substituents. In many cases, the condensation products were obtained in high yields (Table 1).

The electronic effects of phenyl ring substituents were also explored. The experimental results showed the presence of electron-withdrawing or -releasing groups on the substrates had only a slight influence on the yields. The impact of the simultaneous microwave and ultrasound irradiation, microwave irradiation, ultrasound irradiation, and conventional heating has been compared and results are summarized in Table 2.

The results showed that, in accord with our original expectation for this study, the SMUI reaction proceeded much faster (*ca.* 28 times as great as that of under microwave irradiation alone, or 140 times that for sonication alone) and results in comparable or better yields than other methods. This has been made possible thanks to a dramatic enhancement in

Green Context

Alternative energy techniques are important green chemistry tools. Here we see how the combination of two of these—microwave and ultrasonic activation—is effective in the synthesis of aryl acrylic acids. Reactions are carried out in the absence of organic solvents and use inexpensive basic catalysts. Product separation and purification are quite simple and product yields are good. ***JHC***

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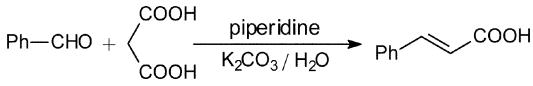
Table 1 Synthesis of 3-aryl acrylic acids through aqueous Knoevenagel–Doebner reaction under SMUI

Entry	Ar	Time/s	Yield (%)[a]
1	C_6H_5	65	87
2	4-ClC_6H_4	60	92
3	4-$CH_3C_6H_4$	65	89
4	4-OHC_6H_4	75	82
5	4-$CH_3OC_6H_4$	95	85
6	4-OH-3-$CH_3OC_6H_4$	70	78
7	3-$NO_2C_6H_4$	75	90
8	4-$NO_2C_6H_4$	70	91
9	2,4-$Cl_2C_6H_3$	65	93
10	Furyl	60	73

[a] All yields refer to isolated products which were characterized by mp data,[1]H NMR and IR spectral analysis.

Table 2 Heterogeneous reaction of benzaldehyde with malonic acid under different conditions



Run	Method	Time	Yield (%)
1	Conventional reflux	7 h	80
2	Microwave (200 W)	30 min	83
3	Ultrasound (50 W) + reflux	2.5 h	79
4	SMUI (mw 200 W+ us 50 W)	65 s	87

mass transfer caused by sonication. Reaction under microwave irradiation was 14 times faster than its counterpart under conventional reflux accompanied with slightly improved yield (83%).

Although there was literature mention that the ammonia (inexpensive, and of low toxicity) catalyzed Knoevenagel–Doebner reaction gave corresponding 3-substituted acrylic acids in good yields,[8] attempts to employ ammonia catalyst (using ammonium bicarbonate as an ammonia precursor) in our experiment failed to give satisfactory yields of desired product. A moderate yield (41%) was obtained of 3-amino-3-phenylpropionic acid[9] which was characterized by mp, IR and ^{1}H NMR spectra.

Due to its characteristics such as nontoxicity, nonflammability, and enormous abundance, water is superior to many other organic solvents from both environmental and economical points of view. In our protocol, the use of water as solvent simplified the final treatment of products. One of the problems of homogeneous reactions run in organic solvents is the separation of products and/or catalysts from the solvents. An additional advantage of the use of water as solvent is that many organic products can be separated by simple filtration or decantation from the resulting mixture. In contrast, the use of organic solvents necessitates tedious and energy-consuming thermal operations such as distillation and rectification distillation, or dilution of the resulting solution with water, which will bring difficulties in solvent recovery.

The experimental procedure is very simple. On completion, the reaction is quenched by acidification with aqueous HCl to precipitate the desired product. Products obtained after recrystallization are of high purity and do not require any chromatographic purification. The piperidine remains in the aqueous phase as a hydrochloride. Simply distilling the water, followed by extracting the residue with NaOH–ethanol, could recover nearly quantitative amounts of piperidine in the aqueous phase.

In conclusion, an efficient, simple and environmentally friendly procedure for the synthesis of 3-aryl acrylic acids from the corresponding aromatic aldehydes has been developed. The procedure does not require organic solvents and furthermore the catalyst can be easily recovered and reused. The science of green chemistry was developed to meet the increasing demand for environmentally benign chemical processes. We believe the combination of sonication and microwave heating will be of importance in the search for green laboratory-scale synthesis. Further investigations of other useful applications related to the microwave and ultrasound combined reaction in aqueous media are in progress.

Experimental

Reactions were carried out in the apparatus described previously.[7] The reagents and solvents are commercially available. All of the products are known compounds and identified by melting point (uncorrected) and spectroscopic data. FTIR spectra were obtained on a Nicolet Nexus 470 infrared spectrometer in KBr discs and ^{1}H NMR spectra were recorded on a 500 MHz Brucker AM 500 spectrometer with TMS as internal standard.

General procedure

To a mixture of aromatic aldehydes (10 mmol), malonic acid (1.25 g, 12 mmol), piperidine (0.34 g, 4 mmol) and K_2CO_3 (0.70 g, 5 mmol) in a 25 mL two-necked flask was added 10 mL of water. The mixture was then subjected to simultaneous microwave and ultrasound irradiation for a specified time (monitored by TLC). The mixture becomes homogeneous during the course of condensation. The reaction was quenched with 1.5 M HCl solution (10 mL) and the precipitate obtained was collected by suction. Recrystallization from aqueous EtOH gives pure product as white or yellowish crystals.

Selected characteristic data are as follows.

Cinnamic acid (1). Mp = 136 °C (lit.[11] 135–136 °C); ν_{max} (KBr, cm^{-1}): 3200, 2900, 2530, 1690, 1625; δ_H (acetone-d_6): 6.55 (t, 1H, CH), 7.15–7.54 (m, 5H, ArH), 7.72 (d, 1H, CH).

4-Methylcinnamic acid (3). Mp = 197 °C (lit.[11] 196–198 °C); ν_{max} (KBr, cm^{-1}): 3280, 2900, 1680, 1630; δ_H (acetone-d_6): 2.54 (s, 3H, CH_3), 6.40 (d, 1H, CH), 7.10–7.55 (m, 4H, ArH), 7.88 (d, 1H, CH).

3-Methoxy-4-hydroxycinnamic acid (ferulic acid) (6). Mp = 167 °C (lit.[12] 165.5–166.5 °C); ν_{max} (KBr, cm^{-1}): 3450, 1660, 1610, 1510; δ_H (acetone-d_6): 3.81 (s, 3H, CH_3), 6.36 (d, 1H, CH), 6.78–7.28 (m, 3H, ArH), 7.50 (d, 1H, CH).

4-Nitrocinnamic acid (8). Mp = 288 °C (lit.[11] 286 °C); ν_{max} (KBr, cm^{-1}): 3200, 2850, 1680, 1625, 1520, 1360; δ_H (acetone-d_6): 2.65 (s, 1H, OH), 6.80 (d, 1H, CH), 7.71–8.21 (m, 4H, ArH), 8.42 (d, 1H, CH).

2-Furylacrylic acid (10). Mp = 140 °C (lit.[13] 141–142 °C); ν_{max} (KBr, cm^{-1}): 3100, 1710, 1635, 1022; δ_H (acetone-d_6): 6.23 (s, 1H, CH), 7.38 (s, 1H, CH), 6.67–7.75 (m, 3H, ArH).

3-Amino-3-phenylpropionic acid. Mp = 216–218 °C (lit.[14] 220 °C); ν_{max} (KBr, cm^{-1}): 3010, 2610, 2205, 1625, 1580; δ_H (D_2O): 2.45 (d, 2H, CH_2), 4.02 (t, 1H, CH), 7.28–7.41 (m, 5H, ArH).

Acknowledgements

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Green solution for tannery pollution: effect of enzyme based lime-free unhairing and fibre opening in combination with pickle-free chrome tanning

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Growing global concern on environmental health is forcing all the processing industries to adopt greener and cleaner manufacturing practices. Thus, the leather industry is being pressurized to look for cleaner leather processing. The conventional method of leather making involves do–undo logic. This results in the emission of a huge amount of pollution load such as biochemical oxygen demand (BOD), chemical oxygen demand (COD) and total solids (TS). Currently tanners are looking for design and utilization of cleaner and safer technologies. In this approach, a process has been designed to limit the pH range in leather processing from 13.5–2.8 to 8.0–3.8. An experimental process has been developed by combining enzymatic unhairing, enzyme based fibre opening and pickle and basification free chrome tanning. The experimental tanning process provides comparable leather quality with reduced environmental impact and effluent treatment costs. The process explored also appears to be economically viable.

Introduction

The leather industry is under pressure from environmental authorities to comply with pollution and discharge legislations. Thus, the leather industry is being pressurized to look for cleaner options for processing raw hides and skins. Conventional methods of preparatory and tanning processes discharge enormous amounts of pollutants.[1] Leather processing involves a number of unit operations, as shown in Fig. 1. Generally, the conventional conversion process of hides to leather involves 'do–undo' operations like, curing (dehydration)–soaking (rehydration), liming (swelling)–deliming (deswelling), pickling (acidification)–depickling (basification).[2] Further, the skins or hides are subjected to wide variations in pH 13.5–2.8.[3] Such changes in pH demand the use of acids and alkalis, which lead to the generation of salts. This results in a net increase in TDS (total dissolved solids) comprising chlorides, sulfates and other minerals in tannery wastewaters.[4] Also, toxic gases like hydrogen sulfide are evolved during the process. Apart from this, solid wastes including sludge from tanneries and chrome sludge from effluent treatment plants are being generated. Questions have already been raised about the negative consequence of pollution from wastewaters, careless disposal of solid wastes and gaseous emissions.[3] This happens to be a major stumbling block for many of the tanners around the world.

Liming and reliming processes are noxious and they contribute 60–70% of the total pollution load in leather processing.[5] In the beam house, it has been reported that the conventional unhairing process with sodium sulfide and lime is responsible for most pollution in leather processing.[6] Lime has the potential to drive swelling in a gradual manner due to its low solubility but does not pose serious environmental concern. Formation of a large amount of lime sludge is the main drawback of lime.[7] The use of ammonium salts for deliming leads to emission of noxious gas (ammonia).[8] The role of salt in pickling is to suppress the acid swelling through ionic strength effects, but it contributes to TDS.[9] The present commercial chrome tanning method gives rise to only about 60–70% chromium uptake.[10,11] This poor uptake results in material wastage and ecological imbalances. The international specification for the discharge of chromium bearing streams from tanneries is less than 2 ppm.[12]

In the present work, an approach has been made to render the tanning activities cleaner through minimizing the discharge of pollutants. This will not only help in the reduction of pollutants, but also reduce the water consumption substantially. Various possible approaches are (a) the use of chemicals having lower toxicity or less environmental impact, (b) recovery of water and valuable chemical inputs from each sectional stream of wastes and reuse in leather processing to as great an extent as possible, (c) near 100% utilization of chemicals, (d) process innovation, (e) product innovation and (f) integration of processes.

A clean and green approach demands that the discharge from any process should be minimized and valuable materials recovered. The present work modifies the conventional process

Green Context

Conventional methods of pre-tanning and tanning in the leather industry discharge enormous volumes of pollutants including salts, toxic metals and toxic gases. The Green Chemistry approach to move towards zero pollutant releases is based on the use of non-hazardous treatment chemicals, the recovery of chemicals used (including water) and the integration of processes. In this article a three-step integrated process based on non-hazardous biocatalysts is described. Total solids waste and COD are significantly reduced in a process that is also shown to be economically viable as well as greener. ***JHC***

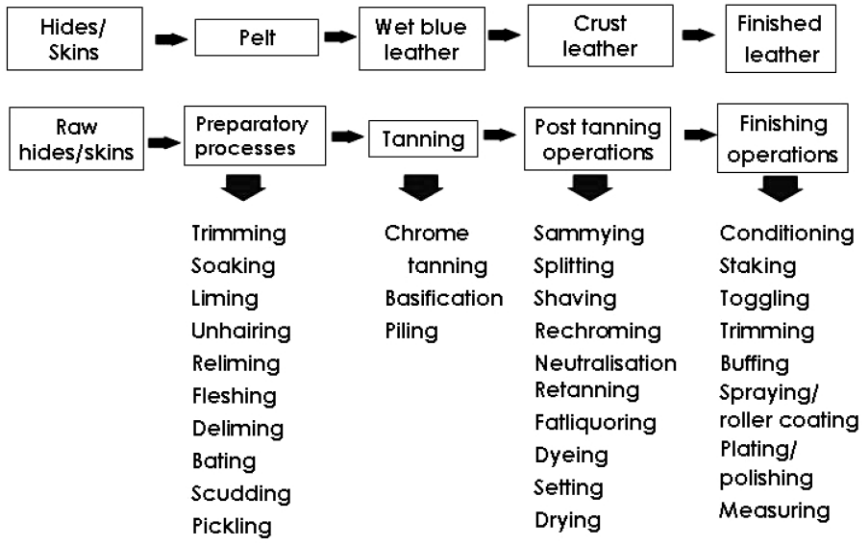

Fig. 1 Various unit processes and operations in leather processing.

and employs lime-free enzymatic unhairing, enzyme based fibre opening and pickle-free chrome tanning. The net benefits envisaged from this approach are reduction in the use of chemicals and cost, with a reduction in utilities like water and power. Elimination of several processes, *viz.*, liming, reliming, deliming, pickling and basification is possible with subsequent reduction in process time, TS, COD, sludge volumes (total elimination of lime sludge) and also better exhaustion of chromium in tanning.

A lime-free enzymatic dehairing process using a reduced amount of sodium sulfide has been standardized for cowhides, which ensures complete dehairing within 18 hrs.[13] The dehaired pelt looks clean and white in color without any scud. However, this grain side application is difficult for goatskins due to their dense hair arrangement. Enzyme based dehairing for goatskins, completely free of lime and sodium sulfide has now been established using drum application.[14] However, the extent of opening up of fibre bundles was not adequate for the production of various kinds of leathers. The pelt requires reliming/alkali treatment for its future function. The use of lime in reliming creates lime sludge, COD and TS. Enzymes have been widely used in leather manufacture in soaking, dehairing, bating and degreasing processes.[15] Recently, enzyme based opening up of fibre bundles has been standardized for cowhides and goat skins.[16,17] Enzymes are exemplary agents of green technology. This process leaves the skin or hide matrix with a pH of 8.0. Hence, the deliming process is not needed. Salt free pickling using naphthalene sulfonic acid is well known and extensively studied.[18] A pickle-free tanning system using chrome syntan and modified BCS (basic chromium sulfate) has been established[19,20] A pickle and basification free tanning system using commercial BCS and polymeric syntan has been reported.[21] In the present approach, a pickle–basification free chrome tanning process has been employed for tanning goatskins that have been previously dehaired using a standardized enzymatic dehairing process[14] and opened up using a standardized enzymatic fibre opening process.[17] Hence, in this work, the entire preparatory and tanning processes have been modified to achieve clean and green leather processing through the use of enzymes for lime-free unhairing and fibre opening combined with pickle-free chrome tanning. The physical characteristics, hand evaluation and scanning electron microscopic (SEM) analysis of both experimental and control leathers have been carried out. Composite liquors from both the processes have been analyzed for COD, TS, and chromium. Comprehensive input–output audits and a techno-economic viability study have also been carried out for both the processes.

Results and discussion

Input–output audit of the experimental and control process

The input–output audit in leather manufacture is to assess the effectiveness of the developed process against the conventional process. The input and output of the raw materials, chemicals and water have been monitored for the control and experimental processes. The values have been calculated for processing 1 t of raw skins and are given in Table 1. The reduction in the weight of the soaked skins after liming is mainly due to the removal of hair, epidermis, soluble protein and water and is more or less similar for both control and experimental leathers. In the control process the amount of dry material produced is 150 kg; of which the hair of the goatskins alone constitute nearly 94%. The amount of dry hair produced from the control and experimental processes is about 141 and 148 kg, respectively. In both experimental and control processes, the hair obtained is in undamaged form, which can be further used for several applications. The amount of dry sludge produced from the control process is about 9 kg, whereas the experimental process does not produce any dry sludge. This dry sludge is composed of lime, sodium sulfide and pulped materials dropped from the flesh side of the skins during the dehairing operation. A major portion of the chemicals was carried away with the skins to the reliming process. In reliming/enzyme based fibre opening, the water absorbed by the skin in the case of the control is nearly 38% of the applied water and is 40% in the case of enzyme based fibre opening. In reliming, the amount of dry sludge formed by the control process is 118 kg and there is no dry sludge in the case of the experimental process. It is intriguing to note that there is an excess of materials present in the sludge, since the reliming process employs only 100 kg of lime. The dry sludge formed in the conventional process is primarily due to the lime carried over from liming and further usage of lime during the reliming process. It is evident from Table 1, that 11.6 kg of lime is present in the effluent. This indicates that the remaining 65 kg of lime, nearly 30–35%, is present in suspended form in the effluent.[22] No attempt has been made to analyze the amount of sodium sulfide in the relime liquor. Hence, the application of a negligible amount of enzyme not only avoids the use of a huge quantity of lime but also circumvents the problem of solid waste disposal.

The conventional deliming process employs ammonium chloride and neutralizes the alkalinity. This leads to the formation of ammonia and calcium chloride. At the completion

Table 1 Input-output audit for both control and experimental process[a]

Process	Chemicals/raw material	Control		Experimental	
		Input/kg	Output/kg	Input/kg	Output/kg
Liming/enzyme based dehairing	Soaked skins	1000	800	1000	780
	Water	100	—	100	—
	Lime	100	—	—	—
	Na_2S	30	—	—	—
	Enzyme (SPIC)	—	—	10	—
	Dry hair	—	141	—	148
	Dry sludge	—	9	—	—
Reliming/bio-product for opening up	Dehaired skins	800	1100	780	1090
	Water	3000	2180	780	470
	Lime	100	11.6	—	—
	α-amylase (SPIC)	—	—	2.73	N.E
	Dry sludge	—	118	—	—
Washing	Fleshed skins	780	780	710	710
	Water	1560	1480	1420	1250
Deliming	Fleshed skins	780	N.E	—	—
	Water	780	740	—	—
	NH_4Cl	7.8	R.P	—	—
	Alkali bate	3.9	N.E	—	—
Washing	Delimed skins	780	N.E	—	—
	Water	1560	1520	—	—
Pickling	Delimed skins	780	N.E	—	—
	Water	780	370	—	—
	Salt	78	R.P	—	—
	H_2SO_4	9.36	R.P	—	—
Chrome tanning	Pickled/enzyme treated skins	780	N.E	710	N.E
	Water	546	716	710	685
	Polymeric syntan	—	—	7.1	N.E
	BCS	39	10.92	35.5	1.42
	Sodium sulfate from BCS[b]	—	9.23	—	11.23
	Sodium formate	3.9	R.P	—	—
	Sodium bicarbonate	7.8	R.P	—	—
Washing	Chrome-tanned skins	780	N.E	710	N.E
	Water	1560	1560	1420	1420

[a] Weight of skins before soaking. [b] Assuming that basic chromium sulfate contains 33% of sodium sulfate. R.P – Reaction product; N.E – Not estimated.

of deliming, the pelts are treated with bating enzymes for the removal of non-collageneous proteins. Hence, deliming and bating operations lead to nearly 12 kg of chemical usage and subsequent discharge in the effluent. In the case of experimental pelts, deliming and bating processes were not carried out because both dehairing and fibre opening processes are carried out at pH 8.0 and the purpose of bating has already been met during the enzyme based fibre opening process. The conventional process requires a pickling step for the subsequent chrome tanning process. This process employs nearly 87 kg of chemicals for 1 t of raw goatskins. This leads to the discharge of nearly 87 kg solids into the effluent at one stage or the other. The experimental tanning process does not require sodium chloride and sulfuric acid.

Further, the conventional chrome tanning process requires nearly 12 kg of mild alkali salts (sodium formate and sodium bicarbonate) for the basification (complexing chromium with the protein carboxyl groups) process. These mild alkalis are primarily used to neutralize the acidity. Hence, the pH increases from 2.8 to 3.8, thereby leading to the fixation of chromium with the skin protein. Normally, the BCS contains 33% of sodium sulfate. Hence, the conventional chrome tanning–basification processes lead to the discharge of nearly 32 kg solids comprising about 10.9 kg BCS for processing 1 t of raw goatskins. This emission is reduced to nearly 12.6 kg by employing a pickle and basification free chrome tanning method.

The total amount of chemicals and bioproducts consumed in the control and experimental leather processing is 380 and 55.5 kg, respectively. This means that the experimental leather processing enjoys a reduction in total chemical consumption of 85% compared to the control leather processing. Of the total chemicals and bioproducts used, only the tanning agent is fixed with the skin matrix. The remaining chemicals are discharged in either liquid or solid form. The control and experimental leather processing release 143 and 15 kg materials, respectively (into the effluent), which means a 90% reduction is possible. A major portion of the chemicals is present in the sludge along with proteinaceous matter in the case of conventional leather processing. No attempt has been made to analyze the fraction of chemicals present in the sludge. The dry sludge formed in the case of the control process employing 20% lime[23] for paint liming and reliming as followed in developing countries is about 127 kg. When the amount of lime used in developed countries, 4% for both paint liming and reliming, is considered the dry sludge formed is about 25 kg. However, the lime sludge formation is completely eliminated by employing enzyme based preparatory processes.

Scanning electron microscopic analysis

Scanning electron photomicrographs of crust leather samples from the control and experimental leather processes showing the grain surface of the leathers at a magnification of ×100 are shown in Figs. 2a and 2b. Both the control and experimental leather samples exhibit a clean grain surface, which indicates that there is no grain damage or physical deposition of chromium. Scanning electron micrographs showing the cross section of both control and experimental crust leathers at a magnification of ×500 are depicted in Figs. 3a and 3b. The fibre bundles are evenly dispersed (separation of fibres) in both cases. This shows that the opening up of fibre bundles using lime or enzyme is comparable. However, the fibre bundles seem to be

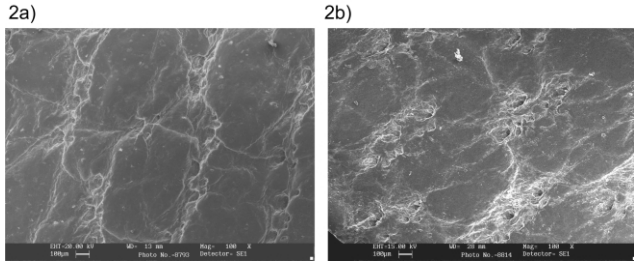

Fig. 2 Scanning electron micrographs of control and experimental crust leather samples showing the grain surface (a) control crust leather (×100) (b) experimental crust leather (×100).

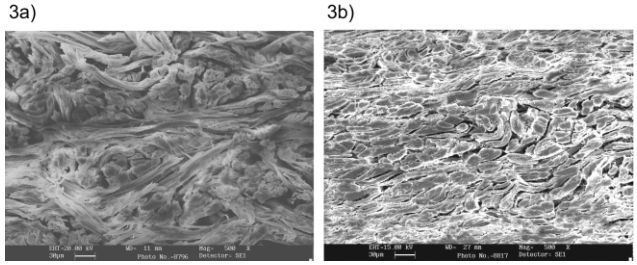

Fig. 3 Scanning electron micrographs of control and experimental crust leather samples showing the cross section (a) control crust leather (×500) (b) experimental crust leather (×500).

compactly woven in the experimental leather sample compared to the control leather sample. This could be due to the high filling nature of polymeric syntan.[19–21]

Chromium in leather

Liming–reliming processes are known to remove non-collageneous proteins and loosen the matrix. Loosening makes it easier for the tanning agent, dyestuff, fatliquors and other substances to diffuse into the skin. Hence, while examining the extent of opening up of fibre bundles it is imperative to look at the chromium content in leather. The percentage of chromic oxide content in wet blue leathers from both control and experimental processes are given in Table 2. Experimental leathers contain a higher percentage of chromic oxide as compared to control leathers. This is evidenced from the increased exhaustion of chromium in the experimental tanning process. This is due to the presence of carboxyl groups of collagen in ionized form at higher pH during the entire course of pickle and basification free chrome tanning.[21,24,25] Details of the mechanism, fixation cum penetration of chromium, are discussed elsewhere.[25] Hence, it is possible to reduce the usage of BCS in the experimental tanning process.

Table 2 Comparison of chromium content in wet blue leathers from control (C) and experimental (E) processes[a]

Sample	% Cr_2O_3/dry weight basis	% Exhaustion
C	2.86 ± 0.12	72
E	3.79 ± 0.07	96

[a] Moisture free chrome-tanned leather weight.

Strength and bulk properties

Tensile and tear strength tests were carried out for all the crust leathers both along and across the backbone line. The mean of the values corresponding to along and across the backbone was calculated. The grain crack strength for all the crust leathers was measured. The average values are given in Table 3. It is seen that both control and experimental leathers exhibit higher tensile, tear, grain crack and bursting strength values higher than those of Bureau of Indian Standards (BIS) norms.[26] Control and experimental crust leathers were evaluated for various bulk properties by hand evaluation. The average of the rating for the five leathers corresponding to each experiment was calculated for each functional property and is given in Fig. 4. Higher numbers indicate better property. The experimental leathers exhibit similar fullness compared to control leathers in spite of the reduced use of synthetic tanning agents during post-tanning. Other properties such as softness, grain tightness and smoothness are comparable to that of conventionally processed leathers. The overall appearance of both control and experimental leathers are comparable.

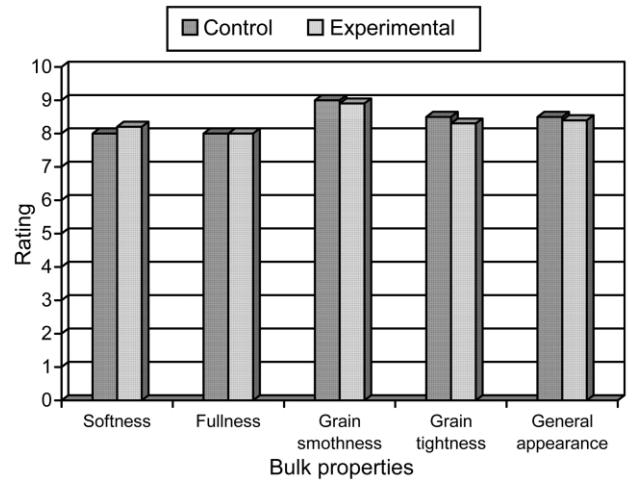

Fig. 4 Hand and visual evaluation data for control (C) and experimental (E) leathers.

Environmental benefits

The composite liquors have been collected from the conventional and experimental tanning processes excluding soaking up to post-tanning. COD and TS are the two parameters that have been chosen for analyzing the environmental impact. A direct

Table 3 Physical testing data of control (C) and experimental (E) leathers

	Tensile strength/ kg cm^{-2}	% Elongation at break	Tear strength/ kg cm^{-1}	Grain crack strength (average value[b])		Bursting strength (average value[b])	
Experiment	average value[a]	average value[a]	average value[a]	Load/kg	Distension/mm	Load/kg	Distension/mm
C	328 ± 5	81 ± 4	86 ± 5	55 ± 1	15 ± 0.3	66 ± 1	16 ± 0.3
E	353 ± 6	73 ± 3	73 ± 2	54 ± 2	13 ± 0.4	65 ± 2	14 ± 0.4
BIS Norms[26]	250	60–70	30	20	7	—	—

[a] Average of mean of along and across backbone. [b] Average of load and distention.

correlation of the observed COD/TS values with the environment may not give proper consequences. Hence, the COD/TS values have been converted into emission loads. The COD and TS values and the calculated emission loads are given in Table 4. The COD and TS emission loads with soaking are given in parenthesis for comparison. The COD and TS values for the experimental leather processing are lower than that of the control leather processing, in spite of the reduced water usage in experimental leather processing.

The reductions in the COD and TS emission loads by the adoption of the experimental tanning process excluding soaking are 52 and 74%, respectively, compared to the control leather processing. These reductions are primarily due to the enzyme based preparatory processes and pickle–basification free chrome tanning. In other words, the presence of part of the sodium sulfide from liming/reliming, oxidisable matter from deliming and pickling and a higher amount of chromium salts from tanning increases the COD load in the conventional leather processing. However, including the contributions from soaking, the reductions are 29 and 31% for COD and TS, respectively. The lower reductions on including soaking are mainly due to the presence of soluble proteins and sodium chloride from the wet salted skins. Although the soaking process contributes nearly 50% of the total TS, liming, reliming, pickling and basification processes cumulatively contribute to TS significantly in the control leather processing. The experimental process eliminates the liming, reliming, deliming, pickling and basification processes and thereby leads to considerable reduction in TS.

Another important pollutant from the tannery wastewater is chromium(III). The chromium uptake is found to be 72 and 96% of the dose for the conventional and experimental tanning processes, as seen in Table 2. The chromium concentration of the spent chrome liquor from the conventional and experimental tanning processes is 1230 and 74 ppm, respectively. Thus, it seems that the concentration of chromium in the composite liquor is 106 and 5 ppm for the conventional and experimental tanning processes. Corresponding emission loads are 0.9 and 0.05 kg of chromium. Hence, the emission load is reduced by 95% in the experimental process. In most countries, a chromium discharge level of 2 ppm is enforced for tanners.[13] Hence, the segregation of the chrome liquor from the main stream is essential. Various options for the management of chromium include reduction in the BCS dose, direct recycling of segregated liquor to the next batch instead of using fresh water or recovery of the chromium using a semi-continuous chrome recovery system and reuse.[27]

Techno-economic viability

Development of any new process requires commercial viability and cost effectiveness. An experimental tanning process has been followed in this work to achieve clean and green leather processing without affecting the quality of the leathers. The amount of water employed for both control and experimental leather processing is given in the Table 5. It is apparent that the experimental leather processing enjoys a reduction in water consumption of 26% compared to the control leather processing. This reduction in water consumption lowers the hydraulic load to the effluent treatment plant (ETP) by 27%, thereby reducing the operating cost of ETP. The consumption of time and energy for the control and experimental processing is given in Table 6. The reduction in time and energy consumption is 68 and 31%, respectively, compared to the control leather processing. It is evident that there is a significant reduction in the consumption of water, energy, and time. This would lead to an overall reduction in the cost of leather processing. The total

Table 5 Comparison of water requirement and discharge for control (C) and experimental (E) leather processing of 1 kg raw skins[a]

	Control		Experimental	
Unit processes	Input/kg	Output/kg	Input/kg	Output/kg
Soaking	9.0	8.0	9.0	8.0
Liming/enzyme based dehairing	0.1	—	0.1	—
Reliming/enzyme based opening up	3.0	2.180	0.78	0.47
Washing	1.560	1.480	1.42	1.25
Deliming and bating	0.780	0.74	—	—
Washing	1.560	1.520	—	—
Pickling	0.780	0.370	—	—
Chrome tanning	0.546	0.716	0.78	0.685
Washing	1.560	1.560	1.420	1.420
Washing	0.630	0.540	0.55	0.42
Neutralization	0.630	0.620	0.55	0.52
Washing I	0.420	0.410	0.37	0.36
Washing II	0.420	0.430	0.37	0.37
Post-tanning	0.620	0.590	0.52	0.5
Washing	0.420	0.420	0.37	0.38
Total	22.026	19.576	16.23	14.375

[a] Weight of skins before soaking.

Table 6 Time and power consumption for the conventional (C) and experimental tanning (E) processes

	Time/h		Hours consuming power	
Unit operations	C	E	C	E
Liming/enzyme based dehairing	18	18	—	0.5
Reliming/enzyme based opening up	48	2.5	1.0	2.5
Washing	0.16	0.16	0.16	0.16
Deliming and bating	2.0	—	2.0	—
Washing	0.16	—	0.16	—
Pickling	1.67	—	1.67	—
Chrome tanning	4.0	3.0	4.0	3.0
Washing	0.16	0.16	0.16	0.16
Total	74.15	23.82	9.15	6.32
Total power consumption/kWh			274.5	189.6
Cost/US$			23.5	16.25

@1 h running = 30 kWh; 1 kWh = Rs 4.20; 1 US$ = Rs. 49.00

Table 4 Composite liquor analysis[a]

Process	COD (ppm)	TS (ppm)	Volume of effluent/L t^{-1} of raw skins[b]	Emission load/kg t^{-1} of raw skins[b] processed	
				COD	TS
C	2425 ± 18	15350 ± 42	11576	28 (48)	178 (428)
E	2122 ± 12	7339 ± 23	6375	14 (34)	47 (297)

[a] Composite liquors were collected up to post-tanning excluding soaking. [b] Weight of skins before soaking. Values in parenthesis include COD and TS contributions from soaking. C – Control leather processing; E – Experimental leather processing.

chemical costs for processing 1 t goatskins through the conventional and experimental processes are given in Table 7.

Table 7 Cost estimates of the conventional (C) and experimental tanning (E) processes

	Control	Experiment
Unit operation	(US$/t of raw skins)	
Lime	24.48	—
Sodium sulfide	10.20	—
Biodart (SPIC)	—	24.48
α-amylase (SPIC)	—	15.9
Ammonium chloride	1.35	—
Alkali bate	5.71	—
Sodium chloride	3.18	—
Sulfuric acid	1.14	—
Polymeric syntan	—	10.14
BCS	23.87	21.7
Sodium formate	1.63	—
Sodium bicarbonate	2.22	—
Total	73.78	72.22

It can be seen that both the experimental and control processes possess comparable chemical cost for the production of chrome tanned leathers from 1 t of raw goatskins. However, a possible reduction in the use of BCS in the experimental tanning process provides a cost reduction to some extent. The experimental process would lead to an additional saving of US$19 due to a 30% reduction in the use of synthetic tanning agents during post-tanning. This reduction of syntans is due to the usage of polymeric syntan during chrome tanning. Another major advantage of the experimental process is that it involves enzymatic dehairing and fibre opening, which increases the area of the final leather by about 2%.[13,23,28] This would lead to a saving of US$110 per metric ton of goatskins processed. In total, the experimental leather processing provides a net saving of US$138 per metric ton of goatskins compared to the control leather processing, apart from other indirect economic benefits.

Comparison with process followed in developed countries

Considering the process followed in developed countries, where about 2% lime for paste liming, 2% lime for reliming and 8% sodium chloride for pickling are employed, the application of the experimental tanning process leads to a reduction in chemicals usage of 73%, TS load of 69% excluding soaking and 30% including soaking and complete elimination of the formation of 25 kg dry sludge. Consequently, the overall saving is US$116 for processing one metric ton of raw skins.

Conclusion

Ecological concerns have become key issues in the present global industrial activities. In this context, cleaner leather processing with an approach towards near zero discharge will be the most appropriate theme for sustainable growth in the leather industry. In this investigation, an experimental process has been explored using optimized enzymatic dehairing,[14] fibre opening[17] and pickle and basification free chrome tanning.[21] Input–output audit analysis reveals that the experimental leather processing is able to reduce the total chemical consumption by 85% compared to control leather processing followed in developing countries and 73% in the case of developed countries. In the case of chemical load in the effluent, the envisaged process provides a 90% reduction compared to the control leather processing. The high chrome uptake enables a lower chrome usage in the case of the experimental process. The possible reduction of 32% chrome consumption in this case implies a realistic option for a chemical cost reduction of US$7 per metric ton of salted hides. Scanning electron microscopic analyses of both control and experimental leather samples show that the extent of hair removal is complete with a clean grain surface and good separation of fibre bundles. The strength and tactile properties of the experimental leathers are comparable to that of the control leathers. One of the main advantages of the present approach is the substantial environmental benefit achieved. Composite liquor analysis shows that COD and TS loads are reduced by 52 and 74% excluding soaking and 29 and 31% including soaking. The techno-economic feasibility study shows that the experimental tanning process is able to provide a net saving of US$138 for processing 1 metric ton of goatskins in developing countries and US$116 in developed countries, apart from reducing the effluent treatment cost. The results of this semi technical investigation point to the feasibility of practical leather making by means of a more clean and green process. The gathering of field experience will be the next logical step to reliably confirm the interest of the results and to assess the magnitude of the benefits anticipated on a technical scale.

Experimental methods

Materials

Wet salted goatskins were chosen as raw material. Since this work involves study of the extent of hair removal, opening up of fibre bundles and chromium distribution, more compact goatskins of larger area (0.37–0.56 m^2) were chosen. All chemicals used for leather processing were of commercial grade. Biodart (a dehairing enzyme based on alkaline bacterial protease) and α-amylase (activity 3000 units g^{-1}) were sourced from Southern Petrochemical Industries Corporation (SPIC) Limited, Chennai, India. The chemicals used for the analysis of leather and spent liquors were of analytical grade.

Conventional tanning process (as followed in India)

Ten wet salted goatskins were taken and soaked conventionally. The wet weight after soaking was noted for each skin and termed as the soaked weight. Five skins were taken for controls and five skins for experiment. Five soaked goatskins were paint limed using 3% sodium sulfide, 10% lime[23] and 10% water (percentages based on weight/soaked weight). A thick paste was made using the above composition and applied on the flesh side of the skins. The pasted skins were piled facing flesh side of one skin to the flesh side of the other and left undisturbed overnight. Next day, the skins were dehaired using conventional beam and blunt knife technique. Subsequently, the skins were relimed using 10% lime[23] and 300% water in a drum (percentages based on weight/soaked weight). The drum was run for 5 min every hour for a period of 6 h and left undisturbed for 18 h. Next day, the above process was repeated. Then the pelts (skin without hair) were fleshed, scudded (removal of remnants of epithelial tissue, short hair, dirt, *etc.*, left in the grain surface after dehairing using a blunt knife) and the fleshed weight in the wet condition was noted. The pelts were washed with 200% water (percentage based on weight/fleshed weight) for 10 min. Subsequently, the pelts were delimed by treating with 100% water and 1% ammonium chloride for 90 min. Completion of deliming was ascertained by checking the cross section of the delimed pelt for colorless to phenolphthalein indicator. Bating was carried out in the same bath for 30 min by the addition of 0.5% commercial alkali bate (percentage based on weight/fleshed weight). The bated pelts were washed with 200% water

for 10 min. Pickling was carried out by treating the pelts initially with 100% water and 10% sodium chloride for 10 min followed by the addition of 1.2% sulfuric acid (percentages based on weight/fleshed weight) in three installments at 15 min interval and finally run for 1 h. The pH of the cross section was found to be 2.8. Chrome tanning was initiated by the addition of 5% BCS after draining out 50% of the pickle liquor. The drum was run for 1 h after which complete penetration of chromium was ascertained and 50% water was added. After 30 min running, basification was carried out by the addition of a mixture of 0.5% sodium formate, 1% sodium bicarbonate and 20% water (percentages based on weight/fleshed weight) in three installments at 15 min interval. Finally, the drum was run for 2 h, at the end of which the pH of the cross section of the tanned leather was found to be 3.8. The chrome-tanned skins were washed with 200% water (w/w) for 10 min.

Experimental tanning process (E)

Five soaked goatskins were mixed with a solution comprising 10% water and 1% Biodart (percentages based on weight/soaked weight) in a drum.[14] The drum was run for 5 min every hour for a period of 3 h and left undisturbed for 15 h. The total duration of treatment was 18 h. Next day, the skins were dehaired using conventional beam and blunt knife technique. The dehaired wet weight was noted. Instead of a conventional reliming process, the skins were treated with 0.35% α-amylase and 100% water in a drum (percentages based on weight/dehaired weight).[17] The duration of treatment was 2.5 h. The pelts were then fleshed and scudded. The fleshed weights of the skins were noted. The pelts were washed with 200% water (percentage based on weight/fleshed weight) for 10 min. The pH of the cross-section of the pelt was found to be 8.0. A pickle–basification free chrome tanning was followed[21] by treating the pelts with 100% water, 1% polymeric syntan and 5% BCS (percentage based on weight/fleshed weight). The drum was run for 3 h after which complete penetration of chromium was ascertained. The pH of the cross-section of the pelt was found to be 3.8. The chrome-tanned skins were washed with 200% water (w/w) for 10 min.

The leathers from the control and experimental processes were piled for 24 h. The leathers were then sammed (removal of free water by pressing the wet chrome tanned leather between two felt rollers) and shaved to uniform thickness (1.1–1.2 mm). Rechroming was not done. A conventional post–tanning process was adopted in order to convert the tanned leathers into crust upper leathers, except that the use of synthetic tanning agents was reduced by 30% for the experimental leathers.

Input–output analysis

A comprehensive input–output audit for the raw materials, water, chemicals and other reaction products was carried out for the conventional and experimental tanning processes excluding soaking and post-tanning processes. The amount of dry sludge was estimated as per the procedure described earlier.[22] The mass balance for the acid and base was not calculated since they remain in the effluent in the form of reaction products. Similarly, auditing for enzymes was also not carried out as they are neither absorbed nor fixed with the skin matrix. The amount of chromium in the wastewater from chrome tanning was analyzed as per the standard procedure[29] and the mass balance was calculated based on the volume of chrome liquor collected.

Scanning electron microscopic analysis

Samples from experimental and control curst leathers were cut from the official sampling position.[30] The specimens were cut with uniform thickness without any pretreatment. The specimens were then coated with gold using an Edwards E306 sputter coater. A Leica Cambridge Streoscan 440 scanning electron microscope was used for the analysis. The micrographs for the grain surface and cross section were obtained by operating the SEM at an accelerating voltage of 20 KV with different magnification levels.

Chromium content in leathers

Samples from the official butt portion[30] of experimental and control wet blue leathers were taken for chromium estimation. A known weight (~ 1 g) of the sample was taken and the amount of chromium was estimated as per standard procedure.[31] Samples were initially analyzed for moisture content[32] and chrome content was expressed on dry weight basis of leather.

Physical testing and hand evaluation of leathers

Samples for various physical tests from experimental and control crust leathers were obtained as per IUP method.[30] Specimens were conditioned at 27 ± 2 °C and 65 ± 2% R.H. over a period of 48 h. Physical properties such as tensile strength, % elongation at break, tear strength and grain crack strength were examined as per the standard procedures.[33–35] Experimental and control crust leathers were assessed for softness, fullness, grain smoothness, grain tightness (break) and general appearance by hand and visual examination. The leathers were rated on a scale of 0–10 points for each functional property by experienced tanners, where higher points indicate better property.

Analysis of spent chrome liquor

Spent chrome liquor was collected from both control and experiment processes. Liquors were analyzed for chromium as per the standard procedures.[29] The percentage of exhaustion of chromium was calculated from the amount of spent liquor collected.

Analysis of composite waste liquor

Composite liquors from control and experimental leather processing were collected from all unit operations up to post-tanning except soaking and analyzed for COD and TS (dried at 103–105 °C for 1 h) as per the standard procedures.[32] Drain-off wastes from unhairing and scudding operations were not included during the collection of composite liquor for both control and experimental processes. From this emission loads were calculated by multiplying concentration (mg L^{-1}) by volume of effluent (L) per metric ton of raw skins processed.

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Vacuum-driven lipase-catalysed direct condensation of L-ascorbic acid and fatty acids in ionic liquids: synthesis of a natural surface active antioxidant

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L-Ascorbic acid (vitamin C) is a useful natural antioxidant, but is highly polar and does not dissolve in fats and oils. One solution is the synthesis of 6-*O*-L-ascorbyl fatty acid esters, which are surface-active and protect fats and oils from oxidation. Previous syntheses of 6-*O*-L-ascorbyl fatty acid esters by *Candida antarctica* lipase B (CAL-B)-catalysed esterification were inefficient due to either the poor solubility of L-ascorbic acid in nonpolar organic solvents or poor lipase activity in polar organic solvents. We report that replacing organic solvents with ionic liquids such as 1-alkyl-3-methylimidazolium tetrafluoroborates makes this synthesis more efficient and greener for three reasons. First, like polar organic solvents, ionic liquids dissolve polar substrates such as ascorbic acid (*e.g.*, ~130 mg mL^{-1} in sBMIM·BF_4 at 60 °C), but unlike polar organic solvents, ionic liquids do not inactivate CAL-B. For this reason, using an ionic liquid as the solvent gave a faster reaction and a higher yield of product. Second, it eliminates toxic organic solvents that easily evaporate. Third, since ionic liquids are not volatile, we could use vacuum to drive the equilibrium toward product formation. This ability eliminated the need to use an excess of acyl donor or an activated acyl donor. One problem we encountered was product inhibition due to its precipitation on the immobilized lipase particles. To avoid this inhibition, we added a hydrophobic phase such as hexane or polypropylene beads. A CAL-B-catalysed direct esterification of stoichiometric amounts of ascorbic acid and oleic acid gave a high conversion (83%). The product 6-*O*-L-ascorbyl oleate was isolated as a mixture with oleic acid using only water and ethanol or methanol in 61% yield.

Introduction

Although L-ascorbic acid is a widely used natural antioxidant, its polar nature limits its application in cosmetics and other fats and oils. However, the fatty acid esters of L-ascorbic acid are amphiphilic and can protect fats and oils from oxidation by coating the fat surface with antioxidant. In addition, 6-*O*-L-ascorbyl fatty acid esters are antimutagens and antitumor-promoters.[1] Synthesis of fatty acid esters of L-ascorbic acid requires mild conditions to prevent oxidation of both L-ascorbic acid and its esters, and requires high regioselectivity for the 6-*O*-position.

Several groups have reported *Candida antarctica* lipase B (CAL-B)-catalysed synthesis of ascorbyl fatty acid esters in polar organic solvents such as acetone or tertiary alcohols. Direct condensation of ascorbic acid with fatty acids or transesterification with fatty acid methyl esters gave only modest yields, even with a large excess of acyl donor. For example, Humeau *et al*. reacted a nine-fold excess of methyl palmitate with ascorbic acid in 2-methyl-2-butanol to a maximum of 40% yield.[2] Watanabe *et al*. condensed a five-fold excess of eicosapentaenoic acid with L-ascorbic acid in acetone to a maximum of 47% yield.[3] Using the more expensive fatty acid vinyl esters gave higher yields. Yan *et al*. reacted a three-fold excess of several vinyl esters with ascorbic acid in acetone or *tert*-butyl alcohol and achieved 65–91% yield.[4]

The ionic liquids are polar and dissolve polar materials, but, unlike polar organic solvents,[5] did not inactivate the lipase catalyst.[6] These features allow ionic liquids to work more efficiently in lipase-catalysed reactions of polar substrates. Several groups have reported enzyme-catalyzed reactions in ionic liquids.[7–11] Using ionic liquids instead of an organic solvent in enzyme-cataysed reactions has shown several advantages such as increased enantioselectivity[8] and regioselectivity,[9] increased stability of the enzyme,[10] and increased molecular weight of polymers produced.[11]

Our goal in this paper is a greener and more efficient synthesis of 6-*O*-L-ascorbyl palmitate and oleate by replacing the organic solvents with ionic liquids.[12] In addition, ionic liquids are not volatile, so we used vacuum to drive the

Green Context

The use of vitamin C as an antioxidant is naturally attractive. However, its poor solubility precludes it use in fats and oils, and limits attempts to functionalise it. This paper shows that fatty acid esters of vitamin C (which are oleophilic and retain their antioxidant activity) can be prepared readily using enzyme catalysis in an ionic liquid solvent. The ionic liquid allows the retention of enzymatic activity as well as being a good solvent for vitamin C. ***DJM***

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equilibrium toward product formation. This ability eliminated the need to use an excess of acyl donor or an activated acyl donor such as a vinyl ester. Further, we did not use toxic organic solvents to isolate the product, but only water and ethanol or methanol.

Experimental

General

^{1}H NMR spectra were recorded in acetone-d_6 or $CDCl_3$ at 400 MHz (M400, Varian) and 500 MHz (Bruker). An immobilized form of lipase B from *Candida antarctica* (Novozym 435) was donated from Novozymes A/S (Denmark). Other chemicals were purchased from Sigma-Aldrich. In HPLC analysis, the substrates, products, and the internal standard used were identified by comparison of the retention time with that for authentic samples.

Synthesis of sBMIM·BF_4[13] and 2PentMIM·BF_4

The bromide salts, 1-alkyl-3-methylimidazolium bromide, of corresponding ionic liquids were prepared according to the literature procedure.[14] The tetrafluoroborate salts were prepared and purified according to a literature procedure with slight modification. The 1-alkyl-3-methylimidazolium bromide salt (0.40 mol) was added to a suspension of $NaBF_4$ (1.2 equiv, 52.7 g, 0.48 mol) in acetone (150 mL). After stirring the mixture for 48 h at room temperature, the sodium bromide precipitate was removed by filtration and the filtrate concentrated to an oil (~100 mL) by rotary evaporation. The crude product was diluted with methylene chloride (200 mL) and filtered through silica gel (40–50 g). The solution was filtered again through neutral aluminium oxide (30–40 g) to remove trace amounts of silica gel and other acidic impurities from the ionic liquid. Removal of solvent under vacuum yielded a pale yellow oil: yield 60%.

^{1}H NMR (400 MHz, acetone-d_6, δ) of 2PentMIM·BF_4. 9.04 (s, 1H); 7.82 (dd, 1H); 7.72 (dd, 1H); 4.66 (m, 1H); 4.04 (s, 3H); 1.92 (m, 2H); 1.60 (d, 3H); 1.30 (m, 2H); 0.92 (t, 3H). ^{13}C NMR (100 MHz, acetone-d_6, δ): 136.89, 124.22, 120.64, 57.50, 38.70, 36.01, 20.87, 19.15, 13.28.

Esterification of ascorbic acid

Oleic acid (38 μL, 0.12 mmol) or palmitic acid (31 mg, 0.12 mmol), ascorbic acid (18 mg, 0.1 mmol), 9-fluorenone (2 mg), molecular sieve (50 mg), and Novozym 435 (20 mg) were mixed with solvent (0.5 mL of ionic liquids) and stirred at 60 °C under nitrogen. After 24 h, methanol (10 mL) was added and the immobilized enzyme was quickly filtered off to stop the reaction. Analysis of the mixture was performed by high performance liquid chromatography on a C-18 column (4.6 × 150 mm, Supelco, Bellefonte, PA) with isocratic elution using 95% methanol/5% water containing 0.5% acetic acid at 1 mL min^{-1}. Detection was achieved by a UV detector at 254 nm.

Retention time: (void time, 1.9 min) ascorbic acid, 1.92 min; internal standard (9-fluorenone), 2.41 min; ascorbyl oleate, 3.66 min; ascorbyl palmitate, 3.60 min.

Esterification of ascorbic acid using vacuum

Oleic acid (280 mg, 1.0 mmol), ascorbic acid (180 mg, 1.0 mmol), polypropylene beads (100 mg), and Novozym 435 (200 mg) were mixed in 2PentMIM·BF_4 (5.0 mL). The reaction mixture was stirred for 30 h at 60 °C under vacuum (< 1.0 mmHg). After cooling down, the reaction mixture was diluted with ethanol or methanol (20 mL) and enzyme and polypropylene beads were filtered off. Alcohol was removed by rotary evaporation and water (20 mL) was added to the residue to precipitate out the product. The product (white waxy solid) was recovered by filtering over filter paper: yield 61% and purity 67% (mixture of product and oleic acid).

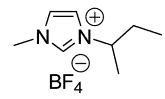
6-*O*-L-Ascorbyl oleate

A sample for analysis was purified by washing with hexane to remove unreacted oleic acid. ^{1}H NMR (500 MHz, CDCl3, δ): 5.40 (m, 2H); 4.86 (d, 1H); 4.45 (m, 1H); 4.26 (d, 2H); 2.81 (m, 3H); 2.40 (t, 2H); 2.15 (m, 4H); 1.65 (m, 2H); 1.30 (br s, 20H); 0.90 (t, 3H).

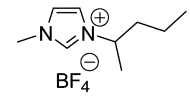
Results

Synthesis of ionic liquids

This paper focuses on two ionic liquids (Chart 1), which we prepared by modified literature procedures. In a previous study,[9] we washed the ionic liquid (diluted with methylene chloride[15] to reduce viscosity) with saturated aqueous sodium



1-(1-methylpropyl)-3-methyl-imidazolium tetrafluoroborate
sBMIM·BF_4



1-(1-methylbutyl)-3-methyl-imidazolium tetrafluoroborate
2PentMIM·BF_4

Chart 1 The best ionic liquids for the CAL-B-catalysed acylation of ascorbic acid with palmitic or oleic acids.

carbonate solution to remove acid impurities that inactivate the lipase. This purification step likely leaves some sodium carbonate in the ionic liquids. Because sodium carbonate may accelerate the oxidation of 6-*O*-L-ascorbyl palmitate or oleate,[16] we modified the purification step. We filtered the solution through neutral alumina instead of washing with sodium carbonate. The ionic liquids purified using neutral alumina gave similar lipase activity, but less oxidation of the produced esters than those purified by washing with aqueous sodium carbonate (see below).

Lipase-catalysed regioselective esterifications of ascorbic acid in ionic liquids

As a model reaction for synthesis of ascorbyl oleate, we used the less expensive palmitic acid and used molecular sieves to remove water and shift the equilibrium toward ester synthesis. We screened four ionic liquids as solvents (Table 1, entries 1–4).

Although structures of all four ionic liquids are similar, one ionic liquid was much better that the other three. After 24 h the conversion in sBMIM·BF_4 (42%) was 1.8–4 times higher than that in MOEMIM·BF_4, PMIM·BF_4, or BMIM·PF_6 (11–24%). Ascorbic acid was dissolved in all ionic liquids,[17] but palmitic acid noticeably dissolved only in sBMIM·BF_4. We hypothesized that the increase yield in sBMIM·BF_4 was due to the increased solubility of palmitic acid in this ionic liquid. To increase the solubility of palmitic acid, we designed a new ionic liquid, 2PentMIM·BF_4, which has an extra carbon as compared to sBMIM·BF_4. Indeed, palmitic acid was more soluble in

Table 1 Initial screening acylation reaction of ascorbic acid in ionic liquids[a]

Entry	Solvent[b]	Conversion[c] (%)	Yield[c] (%)
1	MOEMIM·BF_4[d]	24	18
2	PMIM·BF_4[d]	20	12
3	BMIM·PF_6[d]	11	10
4	sBMIM·BF_4[d]	42	16
5	sBMIM·BF_4[e]	43	40
6	2PentMIM·BF_4[e]	74	53

[a] Conditions: 200 mM of ascorbic acid, 240 mM of palmitic acid, 0.5 mL of solvent, 20 mg of CAL-B (Novozyme 435), 50 mg of molecular sieve 4 Å. 2 mg of internal standard (9-fluorenone), 24 h, 60 °C, under nitrogen, stirred with magnetic stirring bar. [b] Abbreviations: MOEMIM·BF_4, 1-(2-methoxyethyl)-3-methylimidazolium tetrafluoroborate; PMIM·BF_4, 1-propyl-3-methylimidazolium tetrafluoroborate; BMIM·PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate; sBMIM·BF_4, 1-(1-methylpropyl)-3-methylimidazolium tetrafluoroborate; 2PentMIM·BF_4, 1-(1-methylbutyl)-3-methylimidazolium tetrafluoroborate. [c] Conversion and yield were determined by comparison with internal standard by HPLC. Conversion was calculated by the decrease in the amount of ascorbic acid while yield was determined by the increase in the amount of product ester. The deviation was ascribed to oxidation (see text). [d] Purified by washing with saturated aqueous sodium carbonate solution. [e] Purified by filtration through neutral alumina.

2PentMIM·BF_4 and acylation of ascorbic acid in this ionic liquid gave even higher conversion (74% *vs.* 43%, Table 1, entries 5 and 6). The higher conversion (amount of ascorbic acid consumed) as compared to yield (amount of product formed) is presumably due to the air oxidation of the product 6-*O*-L-ascorbyl palmitate.

The time course of the esterification suggested that the produced ester may inhibit the reaction. The reaction rate decreased 3.5-fold after 3 h and a further 2-fold after 10 h (Fig. 1). After 24 h, the conversion was 43%, which is still far from

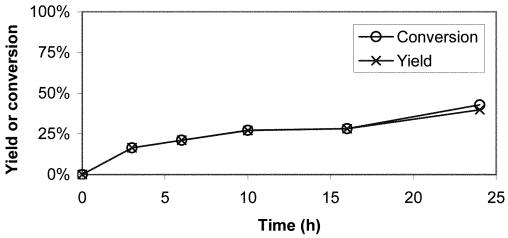


Fig. 1 The time course of the esterification of ascorbic acid with palmitic acid in sBMIM·BF_4. Conditions are same as those in Table 1. Reaction rates: 0–3 h: 0.27 μmol h^{-1} mg^{-1}; 3–6 h: 0.078 μmol h^{-1} mg^{-1}; 6–10 h: 0.075 μmol h^{-1} mg^{-1}; 10–24 h: 0.045 μmol h^{-1} mg^{-1}.

100%. The product, ascorbyl palmitate is poorly soluble in sBMIM·BF_4 – < 5 mg mL^{-1} at 60 °C.[18] After 3 h reaction, the amount of the product (16% yield or ~ 14 mg mL^{-1}) is over the solubility limit. Presumably, the product precipitates on the surface of the immobilized lipase and prevents the substrates from reaching it, thereby inhibiting or stopping the reaction. Releasing the accumulated product from the surface of immobilized lipase would prevent the reaction from slowing down. However, after 16 h, the reaction rate increased slightly. The oxidation product may be more soluble in ionic liquids, and oxidation of the product may eliminate product inhibition. Indeed, when the reaction mixture was not protected from air, the reaction rate did not slow down, but most of the ascorbyl ester product was oxidised (data not shown). In addition, adding the product ester (6-*O*-L-ascorbyl palmitate) at the outset of the reaction in 2PentMIM·BF_4 decreased the conversion (data not shown).

With this assumption, we introduced a hydrophobic additive, hexane or porous polypropylene, to the reaction mixture. These additives are more hydrophobic than the macroporous acrylic resin used for immobilization of CAL-B. The degree of conversion was determined according to different amount of additives (Fig. 2). In both cases there was an optimum amount

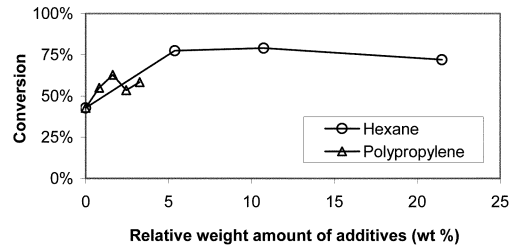


Fig. 2 The effect of hydrophobic additives on the conversion in the esterification of ascorbic acid with palmitic acid in sBMIM·BF_4. Conditions are the same as those in Table 1. The weight amount of the additives (wt%) is relative to the weight amount of the ionic liquid in the reaction. More than 4% of polypropylene beads make it difficult to stir the reaction mixture. Adding more hexane decreased the conversion (56% conversion at 54 wt%).

of additives, 5–11 wt% of the ionic liquid for hexane (50–100 μL) and 2 wt% of the ionic liquid for polypropylene beads (10 mg). The conversion with 5–11 wt% hexane increased by a factor of 2. Similarly 2 wt% polypropylene beads increased the conversion by a factor of 1.5.

We applied the hexane additive to synthesize L-ascorbyl oleate as well as L-ascorbyl palmitate (Table 2). We used sBMIM·BF_4 or 2PentMIM·BF_4 including 20 vol% (11 wt%) hexane as a solvent, molecular sieves to remove water released, and a nitrogen atmosphere to prevent oxidation of the product. The optimized reaction conditions in 2PentMIM·BF_4 gave 83% conversion and 65% yield of ascorbyl oleate (Table 2, entry 4). As in previous work,[12] CAL-B was highly regioselective and formed only 6-*O*-L-ascorbyl oleate without any other regioisomers. In addition, we did not observe any other side-reactions such as hydrolysis of the tetrafluoroborate anion under the reaction condition.

Table 2 Optimized acylation of ascorbic acid[a]

Entry	Solvent	Hydrophobic additives	Acylating reagent	Amount of enzyme/ mg mL^{-1}	Time/h	Conversion[b] (%)	Yield[b] (%)
1	sBMIM·BF_4	hexane, 200 μL mL^{-1}	Palmitic acid	90	14	73	43
2	sBMIM·BF_4	hexane, 200 μL mL^{-1}	Oleic acid	90	14	76	42
3	2PentMIM·BF_4	hexane, 200 μL mL^{-1}	Palmitic acid	90	14	81	44
4	2PentMIM·BF_4	hexane, 200 μL mL^{-1}	Oleic acid	90	14	83	65
5[c]	2PentMIM·BF_4	polypropylene beads, 20 mg mL^{-1}	Oleic acid	40	30	n.d.	61[d]

[a] Reaction conditions were similar to those in Table 1, except the addition of hexane or beads: 200 mM of ascorbic acid, 240 mM of palmitic acid or oleic acid, 0.5 mL of solvents, 45 mg of CAL-B (Novozyme 435), 50 mg of molecular sieve 4 Å. 2 mg of internal standard (9-fluorenone), 60 °C, under nitrogen, stirred with magnetic stirring bar. [b] Conversion and yield were determined as in Table 1. [c] Instead of molecular sieves, vacuum (< 1.0 mmHg) was used to remove water from the reaction mixture: 200 mM of ascorbic acid, 200 mM of palmitic acid or oleic acid, 5.0 mL of solvents, 200 mg of CAL-B, 60 °C, stirred with magnetic stirring bar. [d] Isolated yield.

Vacuum-driven reaction and isolation of product

Removal of water shifts the reaction equilibrium toward product formation. The nonvolatile nature of ionic liquids allowed us to use vacuum instead of molecular sieves to remove the water. We applied vacuum (< 1.0 mm Hg) to the reaction with polypropylene beads for preparation of 6-*O*-L-ascorbyl oleate. The polypropylene beads made the solution more difficult to stir, so we decreased the amount of enzyme from 90 mg mL^{-1} to 40 mg mL^{-1} and extended the reaction time from 14 h to 30 h. Without determining the conversion, we isolated the product with minimal use of organic solvents. To remove the lipase, we diluted the reaction mixture with ethanol or methanol to reduce the viscosity. After filtering to remove the immobilized lipase and polypropylene beads, we concentrated the alcohol solution, and added water to precipitate and isolated 6-*O*-L-ascorbyl oleate with 61% yield (Table 2, entry 5). The isolated product contains unreacted oleic acid (33%), which does not interfere with the antioxidant activity of 6-*O*-L-ascorbyl oleate.

Discussion

The CAL-B-catalysed esterification of ascorbic acid with palmitic or oleic acid works better in ionic liquids than in organic solvents. The yield of 6-*O*-L-ascorbyl oleate is 61–65%, which is higher than similar reactions in organic solvents (40–47% using 5–9 fold excess amount of fatty acids), even though we used only either a stoichiometric amount of oleic acid or its 20% excess. The main reason for the better reaction is the good solubility of the reactants in the ionic liquid combined with the high activity of the lipase in ionic liquid.

Adjusting the structure of the ionic liquid so that it dissolved both reactants was one key to a successful reaction. The two reactants have very different polarities – ascorbic acid is polar, while palmitic or oleic acids are nonpolar. The common ionic liquids dissolved the polar ascorbic acid, but not the fatty acid. Increasing the size of the alkyl chain on the 1-alkyl-3-methyl imidazolium cation increased the solubility of the fatty acids and increased the yield of the reaction.

Purification of the ionic liquid was a second key to a successful reaction. Previous purifications used a wash with aqueous sodium carbonate, but the remaining sodium carbonate accelerated decomposition of the product. An alternative purification using instead of the wash, a filtration through neutral alumina, yielded an ionic liquid that gave high yields.

Both methods for removing water – absorption on molecular sieves or vacuum removal of water – gave similar yields. The vacuum removal is only possible using ionic liquids and not organic solvents. The vacuum removal is greener since it eliminates the recycling of the molecular sieves. One minor problem encountered with the vacuum method was evaporation of oleic acid and its condensation just above the ionic liquid. The evaporation causes oleic acid to separate from the reaction media. Fine-tuning the vacuum may prevent oleic acid from evaporating and thus increase the yield further.

One problem with this reaction was product precipitation. While in many cases product precipitation is desired because it simplifies isolation and shifts the equilibrium toward product formation, in this case it was undesirable since it blocked contact between substrates and catalyst and inhibited the reaction. We solved this problem by adding hydrophobic additives (hexane or polypropylene) to shift the precipitation away from the immobilized enzyme and thereby doubled the conversion of the reaction. One could also imagine a cold region in the reaction vessel where the product would precipitate.

Another problem with this reaction was the rapid air oxidation of the product, 6-*O*-L-ascorbyl palmitate or oleate. Oxidation of ascorbyl esters is three orders of magnitude faster than that for ascorbic acid.[19] We ran only small-scale reactions where it was difficult to completely exclude air. On a larger scale, traces of air would decrease the yield only slightly, so the conversion and yield should be more closely similar.

Researchers often isolate products from ionic liquids using organic solvents. Such processes may not reduce the overall amount of organic solvents used. Although we also used organic solvents to isolate the ascorbyl esters, we used only methanol or ethanol, which are relatively benign organic solvents. We did not focus on removing all the oleic acid from the product because the product is intended as an antioxidant, where the oleic acid would not be a hindrance.

The overall greenness of this reaction is high. The starting materials are natural products and are used in stoichiometric or near stoichiometric amounts. The reaction equilibrium is shifted by vacuum in place of an activated acyl donor or excess acyl donor. The solvent is an ionic liquid, which can be reused in subsequent reactions. To conclude, we found a green method for the preparation of ascorbyl fatty acid esters using only the benign solvents, water, methanol or ethanol to isolate the product.

Acknowledgements

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16 High pH as well as heat, light, or transition metals accelerate the oxidation of ascorbic acid or its esters: M. Y. Jung, S. K. Kim and S. Y. Kim, *Food Chem.*, 1995, **53**, 397; R. H. Bisby, C. G. Morgan, I. Hamblett and A. A. Gorman, *J. Phys. Chem. A*, 1999, **103**, 7454 and references therein. Thus sodium carbonate likely catalyzes oxidation of ascorbic acid and its esters. Indeed, the reaction mixture turned brown when it was not protected from air.
17 Solubility of L-ascorbic acid: >130 mg mL^{-1} in sBMIM·BF_4 and ~ 60 mg mL^{-1} in 2PentMIM·BF_4 at 60 °C.
18 Solubility of ascorbyl palmitate: <5 mg mL^{-1} in sBMIM·BF_4; <10 mg mL^{-1} in 2PentMIM·BF_4 at 60 °C.
19 X. Y. Liu, F. L. Guo, Y. C. Liu and Z. L. Liu, *Chem. Phys. Lipids*, 1996, **83**, 39.

Solid acid catalysts for fluorotoluene nitration using nitric acid

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Fluorotoluenes have been nitrated regioselectively in the liquid phase under mild conditions using solid acid catalysts. Excellent yields were obtained with 70% nitric acid as nitrating agent. Nitration of 2-fluorotoluene at 90 °C showed 55% conversion with 90% selectivity for 2-fluoro-5-nitrotoluene whereas 3-fluorotoluene showed more than 79% conversion even at 60 °C with 67% selectivity for 3-fluoro-6-nitrotoluene and 30% selectivity for 3-fluoro-4-nitrotoluene. In the case of 4-fluorotoluene, side chain nitration was observed instead of ring nitration with 53% conversion and 59% selectivity for 4-fluoro-α-nitrotoluene. Among the different catalysts studied for fluorotoluene nitration, $Fe/Mo/SiO_2$, MoO_3/SiO_2 and H-beta showed higher conversion and selectivity in all three isomers due to higher acidity. A recycling study of catalyst H-beta for nitration of 3-fluorotoluene showed no significant loss in conversion as well as selectivity even after 5 recycles indicating the high stability of the catalyst. Compared to the conventional process, fluorotoluene nitration over solid acid catalysts is a highly regioselective, clean and environmentally friendly process with a simpler work up procedure.

Introduction

Nitration of aromatic substrates is one of the most important and widely studied chemical reactions[1] and has been an active area of industrial chemistry for over a century. The nitration process is used for the production of many commercially important large volume nitroaromatics, which are vital intermediates for dyes, pharmaceuticals, perfumes, and pesticides and hence desired by industry. Despite this, industry still largely relies upon the early technology involving a mixture of nitric acid and sulfuric acid. Mixed acid nitration systems, however, have many disadvantages like low selectivity, overnitration, oxidized product formation and generation of environmentally hazardous waste.[2] Therefore it is essential to have an alternative nitration method, which will overcome these problems. The use of solid acid catalysts is a very attractive alternative because of the ease of separation, recyclability of the catalysts and improved regioselectivity.

Fluoronitrotoluenes are important due to their application as intermediates in the synthesis of antibacterial antibiotics, herbicides, drug intermediates, certain heterocyclics and also as electrophiles.[3–9] Major drawbacks of conventional nitration using fuming nitric acid are low conversion and poor selectivity.[10–12] In recent years there has been a spate of activity aimed at the development of new nitration methods using solid acid catalysts; however very limited success has been achieved. Comparatively very little attention has been given to nitration of fluorotoluenes using solid acid catalysts. Selective nitration of 2-fluorotoluene to produce 2-fluoro-5-nitrotoluene (90%) using nitric acid and acetic anhydride over H-beta zeolite has been reported.[13] However, the explosion hazards of acetyl nitrate and removal of the by-product (acetic acid) are drawbacks for its practical utilization.[12–13] Nitration of 3-fluorotoluene has been achieved using a similar method but with less selectivity for 3-fluoro-6-nitrotoluene (59–61%).[12–13] Lower regioselectivity was observed in the case of 4-fluorotoluene nitration using ionic liquids.[14] In continuation of our earlier efforts on nitration of aromatics,[15–18] the present work deals with nitration of fluorotoluenes and the results are discussed in the following section.

Results and discussion

Catalyst characterization

The MoO_3/SiO_2 catalyst prepared by a sol–gel process using ethyl silicate-40 as silica source showed the mesoporous (pore diameter 78 Å) nature of the material with a surface area of 145 $m^2\ g^{-1}$. The phase purity of the catalysts was investigated by X-ray diffraction analysis. The XRD pattern of H-beta matched well with the literature, confirming its phase purity. The XRD patterns of MoO_3/SiO_2 and $Fe_2O_3/MoO_3/SiO_2$ calcined at 500 °C showed the presence of a MoO_3 crystalline phase without any crystalline silica reflections indicating a high dispersion of MoO_3 on the amorphous silica support. The XRD pattern of B_2O_3/ZrO_2 calcined at 650 °C showed a cubic structure indicating stabilization of zirconia into a cubic phase by addition of boron. The absence of boron oxide peaks in the XRD suggests a high dispersion of B_2O_3 on zirconia. The XRD pattern of $CeO_2/Fe_2O_3/MoO_3$ calcined at 500 °C showed the presence of a two-phase system containing a crystalline MoO_3

Green Context

The nitration of aromatic compounds is one of the classic examples of an organic process where the principles of green chemistry need to be better applied. Hazardous reagents, dangerous waste and the potential for making explosive by-products all add to the difficulties of current processes. Here the use of solid acid catalysts for the commercially important nitration of fluorotoluene is described. The reaction is safer, more efficient and gives less waste. ***JHC***

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phase as the major component and Fe_2O_3 as the minor component without any CeO_2 reflections suggesting the formation of a solid solution or high dispersion of CeO_2 on molybdenum oxide. Fig. 1 shows the results of temperature

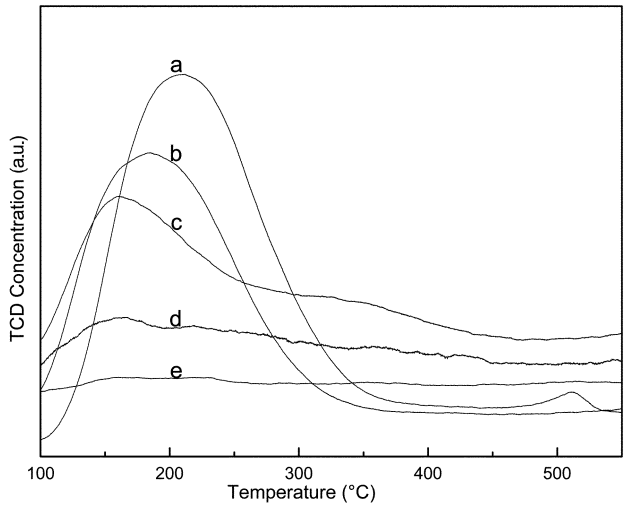


Fig. 1 Temperature programmed desorption of ammonia a) $Fe_2O_3/MoO_3/SiO_2$ b) MoO_3/SiO_2 c) H-Beta d) B_2O_3/ZrO_2 e) $CeO_2/Fe_2O_3/MoO_3$ (TCD = Thermal Conductivity Detector).

programmed desorption (TPD) results of the catalysts which show the acidity of the catalysts to be in the order $Fe/Mo/SiO_2$ > Mo/SiO_2 > H-Beta > B_2O_3/ZrO_2 > Ce/Fe/Mo. However in case of H-beta even though the number of weak acid sites is less, the TPD shows desorption of ammonia at higher temperature suggesting the presence of strong acid sites compared to MoO_3/SiO_2. TPD results also show the presence of a few strong acid sites in the case of $Fe_2O_3/MoO_3/SiO_2$ and a lesser number of weak acid sites as compared to MoO_3/SiO_2.

Nitration reactions

The liquid phase nitration of fluorotoluene was carried out using 70% (w/w) nitric acid in equimolar quantities in the presence and absence of catalysts. The recycling study was done by using H-beta catalyst.

Nitration of 2-fluorotoluene (2-FT). Nitration of 2-fluorotoluene (**I**, Scheme 1) on MoO_3/SiO_2 at 90 °C showed 55.24% conversion, which decreased to 11% when the reaction temperature was 60 °C. No reaction was observed with 30 wt% nitric acid at 60 °C. The results of liquid phase nitration of 2-fluorotoluenes using different catalysts are given in Table 1.

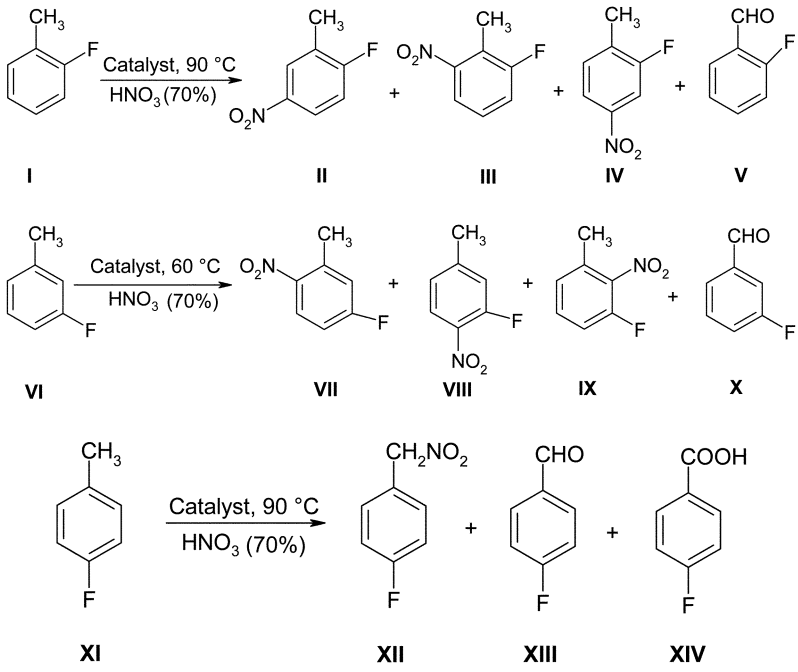
Table 1 Nitration of 2-fluorotoluene (**I**)[a]

Catalyst	2- FT conversion (wt%)	Product selectivities[b]			
		II	**III**	**IV**	**V**
Mo/SiO_2	55.25	88.9	2.7	3.2	5.2
$Fe/Mo/SiO_2$	54.9	84.7	4.1	8.4	2.8
B_2O_3/ZrO_2	35.6	95.6	1.7	1.2	1.5
Ce/Fe/Mo	36.1	90.8	3.7	3.9	1.7
H-Beta	31.8	89.4	3.8	4.7	2.1
Blank	14.7	88.7	4.0	4.3	3.0

[a] Reaction conditions: fluorotoluene/HNO_3 mole ratio = 1.0, HNO_3 (wt%) = 70, catalyst amount = 10% of fluorotoluene weight, temperature = 90 °C. [b] wt% by GC, reaction time = 20 h.

It is seen that maximum conversion of 55.24% with 88.9% selectivity for 2-fluoro-5-nitrotoluene (**II**) over MoO_3/SiO_2 was obtained due to the higher number of acid sites compared to other catalysts. The conversion of 2-fluorotoluene varied from 55.24% to 31.8% for various catalysts indicating the influence of the acidity on the reaction. However, the selectivity for **II** was in the range of 85–95%, which can be attributed to the *para* directing nature of fluorine, with almost no influence of the structure of the acid catalyst. The conversion was very low (15%) when the reaction was carried out in the absence of catalyst.

Nitration of 3-fluorotoluene (3-FT). Nitration of 3-fluorotoluene (**VI**) at 60 °C showed a maximum conversion of 79.2% with 67% selectivity for 3-fluoro-6-nitrotoluene (**VII**) and 29.5% selectivity for 3-fluoro-4-nitrotoluene (**VIII**) with H-beta catalyst. Increase in the reaction temperature from 60 to 90



Scheme 1

°C did not increase the conversion considerably, however the selectivity for nitro products decreased due to formation of oxidation products. The results of liquid phase nitration of 3-fluorotoluene at 60 °C over various solid acid catalysts are shown in Table 2. The conversion was in the range of

Table 2 Nitration of 3-fluorotoluene (**VI**)[a]

Catalyst	3-FT conversion (wt%)	Product selectivities [b]			
		VII	**VIII**	**IX**	**X**
Mo/SiO_2	74.7	62.4	32.4	5.2	0.0
H-Beta	79.2	67.0	29.5	3.5	0.0
$Fe/Mo/SiO_2$	75.3	60.4	33.2	6.4	0.0
B_2O_3/ZrO_2	66.6	66.1	29.5	4.4	0.0
Ce/Fe/Mo	69.7	61.5	31.3	5.9	1.3
Blank	61.0	65.3	29.0	5.7	0.0

[a] Reaction conditions: fluorotoluene/HNO_3 mole ratio = 1.0, HNO_3 (wt%) = 70, catalyst amount = 10% of fluorotoluene weight, temperature = 60 °C. [b] wt% by GC, reaction time = 20 h.

69.7–79.2% whereas the selectivity for nitro products was more or less the same (60–67%). The higher selectivity for **VII** and **VIII** can be attributed to the *ortho* and *para* directing nature of the fluorine and methyl groups. The highest selectivity for **VII** indicates the stronger influence of the *para* directing nature of fluorine as compared to methyl. Conversion increased from 61% to 79.5% when the reaction was carried out in the absence and presence of catalyst respectively.

Nitration of 4- fluorotoluene (4-FT). The liquid phase nitration results are given in Table 3. It is interesting to see that

Table 3 Nitration of 4-fluorotoluene (**XI**)[a]

Catalyst	4-FT conversion (wt%)	Product selectivities [b]			
		XII	**XIII**	**XIV**	Others
Mo/SiO_2	52.6	58.9	6.9	23.6	10.6
H-Beta	42.7	81.0	5.8	4.6	8.6
$Fe/Mo/SiO_2$	38.5	67.9	4.5	23.1	4.5
B_2O_3/ZrO	52.0	67.5	10.9	14.9	6.7
Ce/Fe/Mo	29.6	67.5	8.3	6.2	18.0
Blank	51.1	49.0	5.2	45.8	0.0

[a] Reaction conditions: fluorotoluene/HNO_3 mole ratio = 1.0, HNO_3 (wt%) = 70, catalyst amount = 10% of fluorotoluene weight, temperature = 90 °C. [b] wt% by GC, reaction time = 20 h.

instead of ring nitration, side chain nitration is predominant. In the case of 4-fluorotoluene (**XI**), the *ortho* and *para* directing nature of methyl as well as fluorine strongly influences the nitration reaction. The formation of the side chain nitration product, 4-fluoro-α-nitrotoluene (**XII**), as a main product along with oxidation products such as 4-fluorobenzaldehyde **(XIII)** and 4-fluorobenzoic acid **(XIV)** with the formation of very small ring nitration products was observed. It is clearly seen that in 4-fluorotoluene both *para* positions (*para* to fluorine and methyl group) are occupied and not available for nitration. The positions available for nitration are *meta* either to fluorine or to methyl, which explains the absence of ring nitration products. Side chain nitration has also been observed in the liquid phase nitration of toluene[17] and *o*-xylene[18] with nitric acid using solid acid catalysts. Side chain nitration of polymethylbenzenes has been reported in which the polymethylbenzenes containing methyl groups in positions 1 & 4 often undergo side chain nitration along with ring nitration.[19] Even though in the absence of catalyst the conversion was found be 51%, the oxidation products were formed predominantly (51%) compared to nitration products (49%). This shows that in the absence of catalysts oxidation is favored whereas in the presence of catalyst nitration is favored.

A comparative study of all the three isomers showed, as expected, maximum conversion for 3-fluorotoluene whereas in the case of 4-fluorotoluene preferential side chain nitration was observed rather than ring nitration. This trend in the reactivity is correlated to the availability of the *ortho* and *para* positions with respect to fluorine. In 3-fluorotoluene both these positions are available which results in higher reactivity (70–80% conversion). In case of 2-fluorotoluene both *ortho* and *para* positions with respect to fluorine are *meta* to the methyl group and *vice versa* reducing its reactivity to a considerable extent (31 to 55% conversion). The catalyst structure and acid strength have less influence on conversion and product distribution.

During the recycling study the catalyst H-beta was recycled five times and the conversion of 3-fluorotoluene decreased from 79% to 75% without any appreciable change in product selectivity showing the stability of the catalyst in the reaction environment. The results of the recycling study are given in Table 4.

Table 4 Effect of catalyst recycling [a]

Cycle	Catalyst weight/ mg	Conv. of 3-FT (wt%)	Product selectivities [b]			
			VII	**VIII**	**IX**	**X**
Fresh	220	79.2	67.0	29.5	3.5	0.0
1st	209	79.1	66.8	28.9	4.3	0.0
2nd	197	78.5	68.0	29.2	2.8	0.0
3rd	185	77.1	66.7	30.1	3.0	0.2
4th	174	74.9	65.8	29.7	3.9	0.6

[a] Reaction conditions: catalyst: H-Beta, 3-fluorotoluene/HNO_3 mole ratio = 1.0, HNO_3, (wt%) = 70, catalyst amount = 10% of 3-fluorotoluene weight, temperature = 60 °C. [b] wt% by GC, reaction time = 20 h.

Experimental

Catalyst preparation and characterization

Commercially available H-beta zeolite (Si/Al = 30) was procured from United Catalyst India Ltd. MoO_3/SiO_2 (MoO_3: 20 wt%) was prepared by dissolving 35.28 g of ammonium molybdate in 150 ml hot distilled water and adding it dropwise to a solution of 120 g ethyl silicate-40 (CAS registry No. 18954-71-7) as a silica source in 50 ml isopropyl alcohol with constant stirring. The resulting greenish gel was air dried, ground and calcined at 500 °C in air in a muffle furnace for its use in nitration reactions.

$Fe_2O_3/MoO_3/SiO_2$ was prepared by the same procedure as above with addition of a solution of 5.65 g of ferric nitrate in isopropyl alcohol with constant stirring to the solution of ammonium molybdate. The resulting gel was air dried, ground and calcined. Borate zirconia catalyst was prepared by the procedure reported earlier.[18] The mixed metal catalyst $CeO_2/Fe_2O_3/MoO_3$ was prepared by the procedure mentioned elsewhere.[20]

The catalysts were characterized for their physical and chemical properties using X-ray diffraction analysis (XRD) (Rigaku, Miniflex, Cu-Kα radiation) and temperature programmed desorption (TPD) of ammonia (Micromeritics Autochem 2910). In a general procedure for NH_3-TPD, the catalyst was placed in a quartz tube (0.4–0.5 diameter fraction) and was activated in a helium atmosphere (70 ml min^{-1}) from 30 to 500 °C followed by cooling the sample to 80 °C and a dose of 10% ammonia in helium was passed for 30 min then heated to 100 °C for 10 min to remove physisorbed ammonia. After cooling down to 80 °C, the TPD program (10 °C min^{-1}, up to 750 °C) was started.

Reaction study

All liquid phase nitration reactions were carried out in a batch reactor, under atmospheric pressure. In a typical run: 20 mmol fluorotoluene (2.2 g), 20 mmol nitric acid (1.8 g, 70 wt%) and freshly activated catalyst (10 wt%, 0.22 g, based on fluorotoluene) were continuously stirred in a 50 ml two-necked round-bottomed flask maintained at the required temperature under atmospheric pressure. For the recycling study, after each cycle the catalyst was filtered, washed with acetone, dried at 100 °C and reused for the next cycle. The samples were periodically collected, neutralized with sodium hydrogen carbonate and analyzed by gas chromatography (Perkin Elmer autosystem XL, equipped with capillary column PE-1, 30 m, 0.25 mm ID, 1 μm film thickness and flame ionization detector). Products were also confirmed by GC/MS (SHIMADZU, DB-I column) and GC/IR (Perkin Elmer Spectrum 2001, column: DB-1, 25 m, 0.32 mm ID) and ^{1}H NMR (BRUKER, 500 MHz, using TMS as internal standard in $CDCl_3$).

The side chain nitrated product **XII** was isolated by column chromatographic separation using silica gel (60 mesh) column (3 × 35 cm) using ethyl acetate–petroleum ether (5 : 95) as eluent. A white crystalline product was obtained, yield: 1.02 g, 32%; ^{1}H NMR : δ 5.40 (s, 2 H); δ 7.11 (t, J = 8.34 Hz, 2 H); δ 7.44 (dd, J = 8.34 Hz, 2 H); m/z; 155 (M^+)

Conclusion

Fluorotoluenes are nitrated in the liquid phase in good yields with higher regioselectivity under mild conditions over H-beta zeolite and different solid acid catalysts using stoichiometric quantities of 70% nitric acid. The conversion is governed by the acid strength of the solid acid catalyst and the selectivity by the availability of the *para* position with respect to fluorine because of the stronger *para* directing nature of fluorine compared to methyl. Since the available ring positions in the case of 4-fluorotoluene are *meta* to both fluorine and methyl groups, side chain nitration of methyl group is observed instead of ring nitration. The results of nitration of fluorotoluenes using solid acid catalyst clearly demonstrate the influence of the relative positions of fluorine and methyl on the product distribution.

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Flammability, thermal stability, and phase change characteristics of several trialkylimidazolium salts†‡

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Room temperature ionic liquids (RTILs) have emerged as tunable and potentially "greener" solvents for a multitude of applications. To investigate the solvent properties and potential use as a thermal fluid, a study was initiated to determine the effects of anion type, C-2 hydrogen substitution, and alkyl chain length on the flammability, thermal stability, and phase change characteristics of 1,2,3-trialkylimidazolium room temperature ionic liquids. A Setaflash flashpoint apparatus was used to determine the flammabilities of the RTILs. No flashpoints were detected for any of the imidazolium based RTILs below 200 °C, the maximum temperature of the instrument. The thermal stabilities of the RTILs were measured using the technique of thermogravimetric analysis. The 1,2,3-trialkylimidazolium compounds exhibit slightly higher thermal stabilities than the comparable 1,3-dialkylimidazolium compounds; RTILs with nucleophilic anions decompose about 150 °C lower than RTILs with bulky fluoride containing anions; the alkyl chain length does not have a large effect on the thermal stability of the RTILs; and the pyrolysis decomposition exhibits higher thermal stabilities *via* a different mechanism than the oxidative decomposition. In addition, it was found that although the calculated onset temperatures were above 350 °C, significant decomposition does occur 100 °C or more below these temperatures. The phase change behaviors of several imidazolium based RTILs were characterized by differential scanning calorimetry. The melting points of the RTILs increased with increasing alkyl chain length. Most of the salts studied exhibited significant undercooling, which decreased as the length of the alkyl chain was increased. The hexafluorophosphate and bromide RTILs exhibited polymorphic and liquid crystalline behaviors as the alkyl chain length was increased above C10. The clearing point temperatures increased more rapidly with alkyl chain length than the melting point temperatures.

Introduction

The imidazolium based room temperature ionic liquids (RTILs) have been identified as potential green replacements for volatile organic solvents in a variety of applications.[1–3] These RTILs are good solvent replacements in part because of their relatively high thermal stability, their wide liquidus temperature range, and their apparent nonflammability. Most thermal studies on imidazolium based ionic liquids have focused primarily on the 1,3-dialkylimidazolium salts.[4,5] However, recent investigations have revealed that the 1,2,3-trialkylimidazolium salts appear to be more thermally stable than the corresponding dialkylimidazolium salts.[6] Although it is widely acknowledged that the RTILs have very low flammabilities, there is essentially no quantitative data in the literature supporting this conclusion. Thus, in order to further characterize the thermal properties of the 1,2,3-trialkylimidazolium salts, we have initiated studies on their flammability, thermal stability, and melting characteristics. The nomenclature we use in this paper is shown in Table 1.

Experimental

There are many methods reported for synthesizing imidazolium based RTILs.[3,7,8] For this study, the halides were prepared by

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‡ The policy of the National Institute of Standards and Technology (NIST) is to use metric units of measurement in all its publications, and to provide statements of uncertainty for all original measurements. In this document however, data from organizations outside NIST are shown, which may include measurements in non-metric units or measurements without uncertainty statements. The identification of any commercial product or trade name does not imply endorsement or recommendation by NIST or the United States Air Force (USAF). Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the USAF or NIST.

Green Context

This paper deals with some fundamental properties of a series of ionic liquids. In particular, their thermal stability is very good, with little decomposition below 250 °C, and flashpoints were above 200 °C for all ILs investigated. Trends in properties as a function of structure are observed. Such information is invaluable in evaluating potential solvents for application. ***DJM***

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Table 1 Nomenclature used in this paper

Abbreviation	Definition
BMI	1-butyl-3-methylimidazolium
DMPI	1,2-dimethyl-3-propylimidazolium
DMBI	1-butyl-2,3-dimethylimidazolium
DMDI	1-decyl-2,3-dimethylimidazolium
DMDdI	1-dodecyl-2,3-dimethylimidazolium
DMTdI	1,2-dimethyl-3-tetradecylimidazolium
DMHdI	1-hexadecyl-2,3-imidazolium
TFSI	bis(trifluoromethanesulfonyl)imide

reacting freshly distilled 1-methylimidazole or 1,2-dimethylimidazole with a 5–10% excess of the respective chloro- or bromoalkane in acetonitrile at 60 °C for 3 days. The resulting imidazolium halides were crashed out of solution using ethyl acetate, filtered in a 70–100 μm sintered glass filter, and washed three times with 100 ml aliquots of ethyl acetate. The TFSI, BF_4, and PF_6 salts were prepared *via* an ion exchange reaction by stirring an equimolar mixture of imidazolium halide and LiTFSI, NH_4BF_4, or NH_4PF_6 in acetonitrile at room temperature for 6 days. The solutions were filtered, 15 g carbon black and 15 g basic alumina were added to the filtrates, and the mixtures were stirred for 4 hours. The solutions were sequentially filtered through filter disks of pore size 100, 1.0, 0.45, and 0.1 μm, and the excess solvent was removed using a rotary evaporator. Finally, the resulting ionic liquids or salts were dried under an active vacuum (≤200 mTorr) at 85 °C for 36 hours. In order to remove any residual lithium halide during preparation of the TFSI salt, there were additional steps involving solvent removal, triplicate aqueous wash, and 50 : 50 acetontrile : acetone addition prior to adding carbon black and alumina adsorbents. Elemental analysis was performed by Galbraith Laboratories, resulting in mass errors in carbon analysis ≤1.2%, hydrogen analysis ≤2.9%, and nitrogen analysis ≤2.1% for all of the salts used in this study (Table 2). Flashpoints were measured using a Setaflash, closed cup apparatus with a maximum operating temperature of 200 °C. Thermal stabilities were determined using a TA Instruments, Hi-Res TGA2960 Thermogravimetric Analyzer. 4.0 mg to 6.0 mg samples were placed in open ceramic pans and heated at a scan rate of 10 °C min^{-1} while being purged with 100 ml min^{-1} N_2. For the isothermal TGA study, 5.0 ± 0.1 mg samples of $DMBIPF_6$ were heated as quickly as possible without exceeding the final temperature. For all of the TGA studies, the mean of typically three replicate measurements was reported. The temperatures of both the onset (5% mass fraction loss) and peak mass loss rate have an uncertainty of $\sigma = \pm 4$ °C. The mass loss rate has a relative uncertainty of $\sigma/\bar{x} = \pm 10\%$. Melting and freezing properties were characterized using a TA Instruments DSC2910 Differential Scanning Calorimeter. 3.0 to 5.0 mg samples were transferred to hermetically sealed aluminium pans in a glove box. The samples were heated and cooled at scan rates of 2 or 3 °C min^{-1} while being purged with 25 ml min^{-1} N_2, and data were collected during the second consecutive scan. The melting point and melting enthalpy for indium were within 1% of literature values.

Results and discussion

Thermogravimetric analysis was utilized to investigate the effects of C-2 hydrogen substitution, alkyl chain length, and anion type on the RTIL decomposition temperatures. Results of these experiments are shown in Fig. 1. Similar to the results

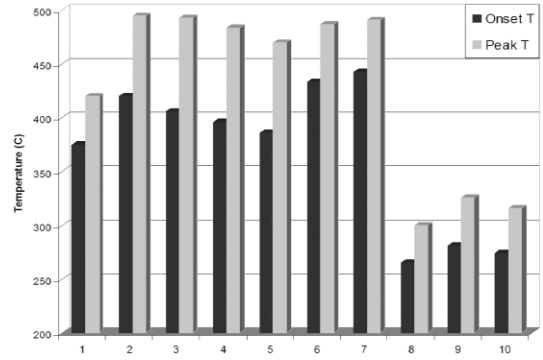

Fig. 1 Decomposition of imidazolium RTILs in N_2 using TGA with a scan rate of 10 °C min^{-1}. (1 = $BMIPF_6$, 2 = $DMBIPF_6$, 3 = $DMPIPF_6$, 4 = $DMDIPF_6$, 5 = $DMHdIPF_6$, 6 = $DMBIBF_4$, 7 = DMBITFSI, 8 = DMBICl, 9 = DMBIBr, 10 = DMBISCN).

reported by Awad *et. al.*, the addition of a methyl group to the C-2 position results in approximately a 40 °C increase in the thermal stability compared to the 1,3-dialkylimidazolium salts.[6] The imidazolium halides exhibit substantially lower thermal stabilities (~150 °C) than the other salts. For most of the imidazolium compounds, the thermal decomposition in nitrogen proceeds by a homolytic mechanism.[6] The halide ions are substantially more nucleophilic than the larger fluoride containing anions and thus decompose by S_N1 or S_N2 nucleophilic decomposition.[6] The length of the alkyl chain does not greatly affect the thermal stability of the imidazolium salt in nitrogen.

It has been established that the imidazolium based RTILs exhibit excellent short term thermal stability. However, Van Valkenburg *et. al.* have suggested that prolonged exposure to temperatures below the TGA determined onset temperatures will result in significant decomposition of the RTILs.[5] To

Table 2 Elemental analysis of trialkylimidazolium RTILs

	Carbon analysis			Nitrogen analysis			Hydrogen analysis		
RTIL	Theoretical	Galbraith	% error	Theoretical	Galbraith	% error	Theoretical	Galbraith	% error
$BMIPF_6$	33.8	33.7	0.3	9.9	10.0	1.0	5.3	5.4	1.9
$DMPIPF_6$	33.8	32.4	1.2	9.9	9.7	2.0	5.3	5.3	0
DMBICl	57.3	57.4	0.2	14.9	14.8	0.7	9.1	9.2	1.1
DMBIBr	46.4	46.5	0.2	12.1	12.0	0.8	7.4	7.5	1.4
$DMBIBF_4$	45.0	45.0	0	11.7	11.7	0	7.2	7.1	1.4
$DMBIPF_6$	36.2	36.3	0.3	9.4	9.4	0	5.8	5.8	0
DMBITFSI	30.5	30.7	0.7	9.7	9.9	2.1	4.0	4.0	0
DMBISCN	56.8	55.2	1.1	20.0	20.1	0.5	8.1	8.3	2.5
$DMDIPF_6$	47.1	47.2	0.2	7.4	7.3	1.4	7.7	7.9	2.6
DMDdIBr	59.1	58.9	0.3	8.1	8.0	1.2	9.7	9.6	1.0
DMTdIBr	61.1	61.1	0	7.5	7.5	0	10.0	9.9	1.0
DMHdIBr	62.9	62.6	0.5	7.0	6.9	1.4	10.3	10.6	2.9
$DMHdIPF_6$	54.1	54.1	0	6.0	6.0	0	8.9	8.9	0

further investigate this effect, we measured the isothermal decomposition rate for $DMBIPF_6$ at several temperatures (*cf.* Table 3). Although the onset temperature determined by

Table 3 Isothermal decomposition of $DMBIPF_6$ from 200 °C–350 °C

Temperature	200 °C	250 °C	300 °C	350 °C
Decomposition rate/% min^{-1}	0.01	0.03	0.25	2.18

nonisothermal TGA was 420 °C, the isothermal experiments clearly show that decomposition occurs at much lower temperatures. Indeed, at 300 °C, the mass loss becomes quite significant, with a mass loss rate equivalent to 15% h^{-1}. There appears to be some decomposition at temperatures as low as 200 °C. However, the mass loss rate at this temperature is close to the error limit of the experiment and any decomposition that does occur at this temperature is likely due to the loss or decomposition of the contaminants, such as water, DMBICl, and NH_4PF_6. We are currently investigating these possibilities.

The flashpoints of several representative imidazolium based RTILs were measured in order to assess their flammabilities relative to other common solvents (*cf.* Table 4). No flashpoints

Table 4 The flashpoints of several common polar aprotic solvents and some "green" solvents given by the manufacturers' MSDS and the flashpoints of RTILs using a Setaflash, closed cup apparatus†

Common polar, aprotic solvents	Flash-point/°C	Imidazolium RTILs§	Flashpoint/°C	
			Measured	Estimated[a]
THF	−14	$BMIPF_6$	≥200	398
AcN	13	$DMPIPF_6$	≥200	450
DMF	58	$DMBIPF_6$	≥200	458
DMSO	89	$DMHdIPF_6$	≥200	430
NMP	93	$DMBIBF_4$	≥200	460
Ethyl lactate	46	DMBITFSI	≥200	467
d-Limonene	48	DMBICl	≥200	283
α-Pinene	32	DMBIBr	≥200	304

[a] Derived from flashpoint-decomposition correlation, σ = ±38 °C.

were detected for any of the RTILs used in this study below the 200 °C limit of the instrument. Furthermore, the imidazolium based RTILs exhibit flashpoints at least 100 °C higher than conventional polar, aprotic solvents and other "green" solvents, such as ethyl lactate, d-limonene, and α-pinene.[9–11] In a recent review, Lyon demonstrated that the decomposition temperature (the average between the onset and peak decomposition temperatures) in N_2 obtained from TGA experiments is approximately equal to the flashpoint for a variety of organic molecules and polymers, as shown in Fig. 2.[12] Assuming this equality holds for RTILs, the actual flashpoints may be estimated from TGA decomposition temperatures. Thus, as shown in Table 4, the approximate flashpoint temperatures for the imidazolium based RTILs are between 250 and 450 °C, depending upon the anion. From these estimates we see that the trialkylimidazolium RTILs with a halide as the anion offer at least a 200 °C improvement in flashpoint over current green solvents, and trialkylimidazolium RTILs with the more stable anions (BF_4^-, *etc.*) most likely offer a 350 °C improvement in flashpoint.

Differential scanning calorimetry was employed to evaluate the effects of C-2 hydrogen substitution, alkyl chain length, and anion type on the RTIL phase change characteristics. These data are shown in Table 5.§ The peak melting point temperature for

§ In order to resolve all of the DSC peaks for the salts exhibiting polymorphic behavior, it was necessary to slow the scan rate from 3 °C min^{-1} to 2 °C min^{-1}.

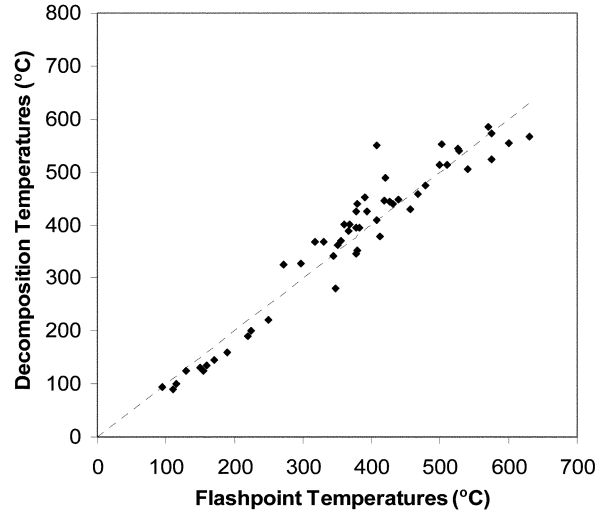

Fig. 2 Correlation between flashpoint temperature and decomposition temperature (data taken directly from ref. 12).

Table 5 Phase change characteristics determined using DSC with a scan rate of 3 °C min^{-1}§

RTIL	T_m[a]/ °C	T_{cryst}/ °C	ΔH_m/ J g^{-1}	ΔH_{cryst}/ J g^{-1}	ΔC_P[b]/ J (g·°C)$^{-1}$
$BMIPF_6$	7.8	−10.8	46.3	37.7	0.39
$DMBIPF_6$	−65.3[c]				
$DMDIPF_6$	42.1	33.8	20.5	20.6	−0.01
	50.0	45.9	19.1	20.3	−0.29
$DMHdIPF_6$	61.3	41.9	37.1	26.5	0.55
	81.8	74.9	68.5	61.3	1.04
	85.1	77.7	10.4	8.9	0.20
	123.3	123.1	1.2	1.2	0
$DMBIBF_4$	−5.9	−54.8	41.7	24.7	0.35
DMBICl	96.8	23.5	97.9	64.9	0.45
DMBIBr	92.7	39.8	86.8	68.8	0.34
DMDdIBr	66.9	24.2	4.5	0.8	0.09
	74.8	48.2	110.4	99.8	0.40
	140.9	137.6	0.8	0.8	0
DMTdIBr	91.1	62.9	119.5	115.3	0.15
	202.6	200.5	0.2	0.2	0
DMHdIBr	97.4	65.5	125.1	126.9	−0.06
	246.3	244.7	0.2	0.2	0

[a] Phase transition temperatures measured at the onset of the peak transition. [b] ΔC_P is the average heat capacity difference between the one phase and the next more ordered one ($\Delta C_P = [\Delta H_m(T_m) - \Delta H_{cryst}(T_{cryst})]/[T_m - T_{cryst}]$).[18] [c] Only a glass transition was observed (T_g was determined using the intercept method).

$BMIPF_6$ (10.4 °C) is in close agreement with that obtained by Dupont *et. al.*[13] Most of the salts show significant undercooling and their heat of crystallization is markedly lower than their enthalpy of melting. This indicates that the heat capacity of the liquid is significantly greater than the heat capacity of the solid (*cf.* Table 5). Replacing the C-2 hydrogen with a methyl group increases the melting point. Increasing the size of the anion generally results in weaker coulombic interactions in the crystal lattice, poor packing of the ions, and a decrease in the melting temperatures (T_m: Cl, Br > PF_6 > BF_4 > TFSI).[14] The most significant change in the phase change behavior occurs when the alkyl chain length is increased, as shown in Fig. 3. Short alkyl chain RTILs exhibit a single melting and crystallization peak (not shown), similar to what has been observed in the 1,3-dialkylimidazolium hexafluorophosphates.[15] Increasing the chain length to C10 introduces polymorphic behavior in the PF_6 salts, as the molecules adopt different types of packing in the crystalline phase. Increasing the chain length to C16 in the PF_6 salt increases the variety of coexisting metastable crystal forms, and introduces liquid crystalline behavior up to 125 °C. In the

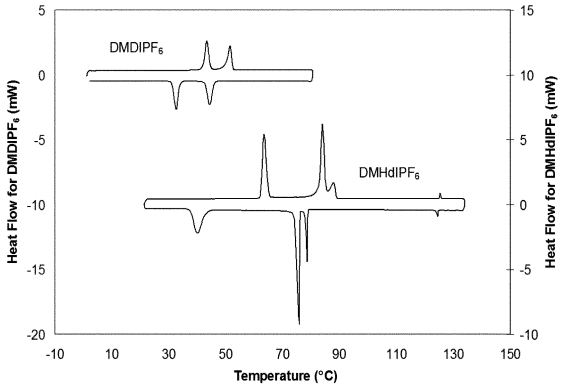

Fig. 3 DSC scan for $DMDIPF_6$ and $DMHdIPF_6$.

bromide salts, liquid crystalline behavior begins at an alkyl chain length of C12. The clearing point temperature increases from 138 °C for DMDdIBr to 246 °C for DMHdIBr. Similar behavior has been observed in the N-alkylpyridinium hexafluorophosphates and di-n-alkyl-dimethylammonium bromides.[15,16] It should be noted that all trialkylimidazolium bromides begin to decompose around 200 °C. Thus, the operational liquid crystalline ranges for the long chain bromides are actually lower than indicated in Table 5. The polymorphism that occurs is in the crystalline state rather than the mesophase as indicated by the undercooling that occurs upon melting.[17]

Conclusions

The thermal study presented here illustrates the wide range of properties possible for imidazolium based RTILs by changing the anion type, alkyl length, or C-2 position substituent. No flashpoints below 200 °C were detected for any imidazolium RTILs used in this study. Based on the correlation between TGA pyrolysis data and ignition temperatures, the flashpoints for imidazolium based RTILs with nucleophilic anions are likely to be between 250 and 300 °C, while imidazolium based RTILs with larger fluoride containing anions are likely to be closer to 450 °C. The decomposition onset temperatures of trialkylimidazolium salts in nitrogen were greater than the analogous dialkylimidazolium salts, and were found to be more dependent upon the anion than the cation. In addition, it was found that although the calculated onset temperatures were above 350 °C, significant decomposition does occur 100 °C or more below these temperatures. The melting points of the imidazolium based RTILs decrease upon an increase in the anion size. Most of the salts studied exhibited significant undercooling, which decreased as the length of the alkyl chain was increased. It was also noted that an increase in alkyl length led to the emergence of polymorphism and liquid crystalline behavior in the unsymmetrical trialkylimidazolium hexafluorophosphates and bromides.

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A green chemistry approach to the synthesis of a crystalline organic inclusion compound

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A large channel supramolecular structure composed entirely of organic molecules has been synthesised using a green chemistry approach, combining mechanochemistry and solid-state photodimerisation. Co-crystals of 1,2-bis(4-pyridyl)ethylene (**bpe**) and benzene-1,2,4,5-tetracarboxylic acid (**bta**) (stoichiometry **bta**·2**bpe**) have been obtained by solid-state grinding of a starting physical mixture. Within the resulting co-crystals, **bpe** molecules are crystallographically arranged such that, after UV irradiation, photodimerisation of **bpe** readily occurs to give a product consisting of **bta** and the photodimer **tpcb**. A large channel structure is then obtained by grinding this mixture of **bta**·**tpcb** in the presence of dimethylsulfoxide.

Introduction

The construction of porous crystalline solids consisting of only organic components as building blocks is currently of interest.[1,2] In the design of such solids, hydrogen bonding is frequently used to create an open framework structure into which, generally, solvent molecules are also occluded. Such design requires an appropriate choice of *node* that can create a two- or three-dimensional arrangement.[2,3] Trimesic acid is often used as such a node in constructing 2-D architectures.[4]

(Re-)crystallisation (and hence filtration and washing) remains an essential step in the preparation of porous crystalline solids. However, appreciation of the fact that there is a need to develop eco-clean processes that reduce waste as well as decrease use of solvents that may be volatile, flammable and/or toxic, requires novel strategies for developing new synthetic methods which either eliminate the use of solvents entirely or significantly reduce the amount involved.[5,6] Here we describe an eco-friendly approach for the preparation of a novel porous organic structure using minimum amounts of solvents.

The use of solid state grinding (mechanochemistry) to allow reaction between two or more components has been established by Toda and others.[7] Indeed, it is now clear that the grinding of two or more organic crystals together is a highly efficient method of making co-crystals whose structures and composition are identical to that obtained by crystallisation from solvent. Such solvent-less "grinding reactions" therefore offer a very attractive way of developing environmentally friendly processes. Furthermore, although some co-crystals appear to form rather slowly, their rate of formation can be significantly enhanced by the simple addition of *minor* amounts of a solvent – significantly lower amounts being used than would be the case for a conventional re-crystallisation.[8]

Co-crystal formation to align molecules for reactivity[9] and in particular the solid-state stereo- and regio-controlled[9] synthesis of the *syn*-dimer of *trans*-1,2-bis(4-pyridyl)ethylene (**bpe**) [*rctt*-tetrakis(4-pyridyl)cyclobutane (**tpcb**)], has been described. In the presence of appropriate linear supramolecular templates, **bpe** molecules can be placed in the crystal such that, under UV irradiation, photodimerisation occurs in a pre-designed manner with high conversion. Various bi-functional[10] and multi-functional[11] molecular templates have been reported and identified. Of interest in this paper is the fact that the product of irradiation, **tpcb**, with the four pyridyl ring placed geometrically on the cyclobutyl rings, is potentially a versatile organic node in the design of organic based porous structures.

Using **tpcb** we now describe a green chemistry approach to the direct solid-state synthesis of a pure organic large channel structure, in which all steps of the preparation have been developed using a minimum amount of solvent. The example uses **tpcb** along with benzene-1,2,4,5-tetracarboxylic acid (**bta**). **bta** serves both as the 'molecular reactor' for the synthesis of **tpcb**, as well as being one of the building blocks for the formation of the porous network (Scheme 1).[11]

Results and discussion

Earlier work has shown that co-crystals of **bpe** and **bta** can be readily obtained from a solution of **bpe** and **bta** in dimethylsulfoxide (DMSO) and the structure of the resulting crystal of **bta**·**2bpe** has been determined by single crystal X-ray diffraction.[11] Analysis confirms that the **bpe** molecules are aligned in pairs, appropriately arranged for efficient photodimerisation. However, co-crystals of a similar composition and potential photoreactivity cannot be obtained by simple grinding of a mixture of **bpe** and **bta** (molar ratio 2 : 1) for 2 h. Fig. 1 indicates the appropriate powder X-ray diffraction patterns. In this case, co-crystal formation by dry grinding (grinding in complete absence of any solvent) is extremely slow. The addition of minor amounts of methanol, however, leads after only 20 min grinding to the complete conversion to **bta**·**2bpe** (Fig. 1(d)) as evidenced by PXRD comparison with the simulated pattern (Fig. 1(e)).[12] (The small amount of methanol

Green Context

Solvent free reactions are of obvious attraction to green chemists. Here, such an approach is utilised to prepare a supramolecular porous array by simple grinding of the two components with an almost "catalytic" amount of solvent in conjuction with photochemical irradiation. This gives a highly regular and porous material in a very simple and direct manner, and avoids the use of more than traces of solvents. ***DJM***

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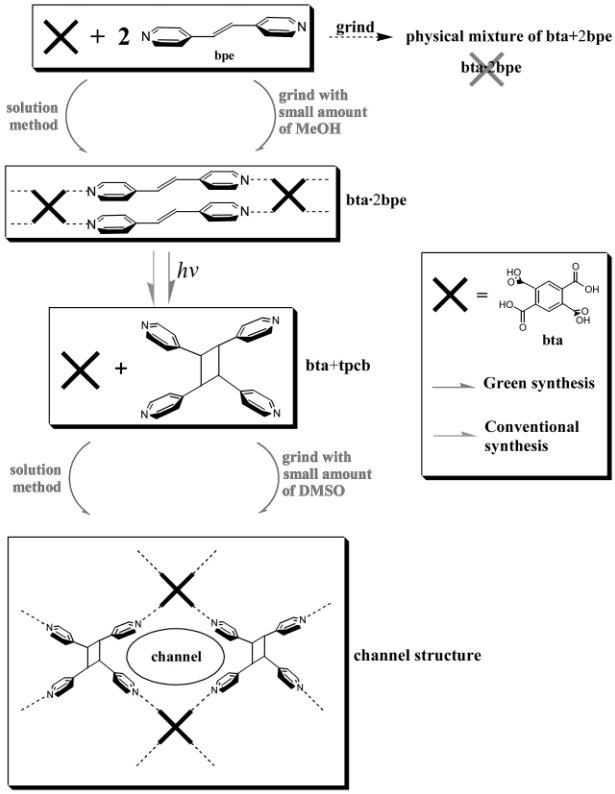

Scheme 1

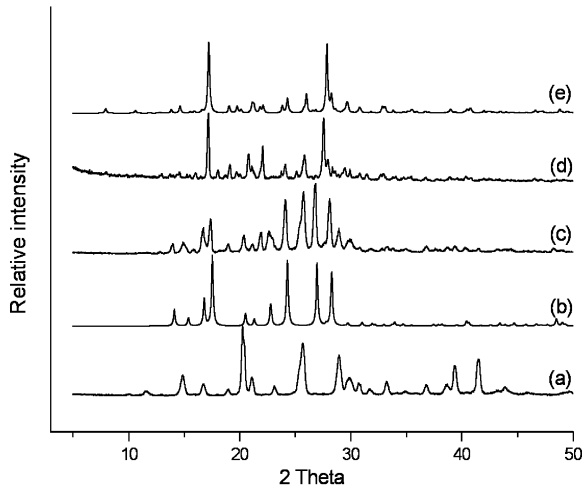

Fig. 1 Powder X-ray diffraction patterns of (a) **bta**, (b) **bpe**, (c) ground mixture of **bta** + 2**bpe** (2 h), (d) ground mixture of **bta** + 2**bpe** with MeOH (20 min) and (e) simulated pattern from single-crystal structure of **bta·2bpe**.

required to form the co-crystal is readily removed by evaporation after grinding.) The co-crystal thus formed after irradiation with UV light results, after 48 h, in close to 100% conversion to **tpcb**, confirmed by ^{1}H NMR analysis (Fig. 2). It is noted that during this photo-induced reaction, there are significant changes occurring within the diffraction pattern, although there is no evidence for separation of the reactants.

Minor amounts of DMSO were then added to the irradiated solid, followed by 20 min grinding. Significant changes are now observed by PXRD after solid-state grinding (Fig. 3). For comparison, single crystals of **bta·tpcb** suitable for full three-dimensional X-ray analysis have been obtained by recrystallisation of the irradiated sample (**bta**+**tpcb**) from DMSO solution. A novel large-size channel (11.0 × 7.8 Å) structure (Fig. 4), where disordered DMSO and water molecules are occupied in

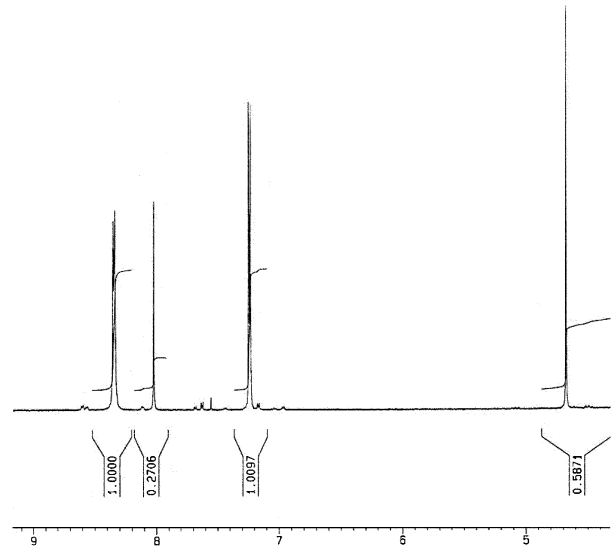

Fig. 2 ^{1}H NMR spectrum of irradiated sample of **bta·2bpe** (**bta** + **tpcb**) [δ = 4.69 (4H, cyclobutyl-H), 7.23 (8H, *meta*-pyridyl-H), 8.02 (2H, **bta**-H), 8.32 (8H, *ortho*-pyridyl-H)].

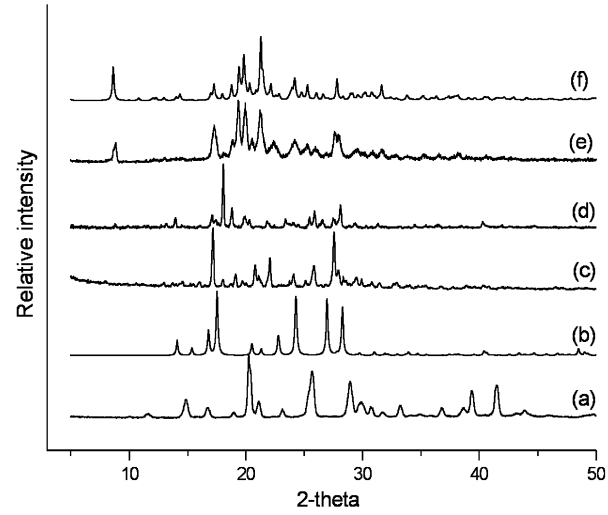

Fig. 3 Powder X-ray diffraction patterns of (a) **bta**, (b) **bpe**, (c) **bta·2bpe** before UV irradiation, (d) **bta·2bpe** after UV irradiation, (e) ground mixture of **bta** + **tcpb** with minor amount of DMSO (20 min) and (f) simulated pattern from single-crystal structure of **bta·tpcb**.

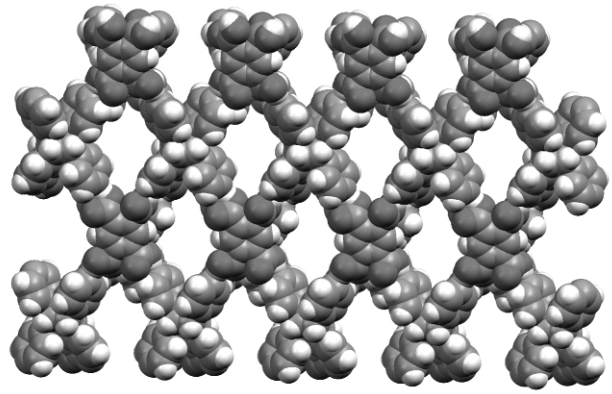

Fig. 4 Projection onto (010) showing the channels in **bta·tcpb**. The 2-D supramolecular networks formed by **bta** and **tcpb** stack in an ABAB arrangement along the *b*-axis. Inclusive DMSO and water solvent molecules have been deleted for clarity.

the channels, is observed in the structure of **bta·tpcb**.[11] It is noted that the PXRD pattern of the ground sample now closely resembles the simulated PXRD of the DMSO solvate **bta·tpcb**. Although there are slight differences in the relative intensities and positions of the reflections between the solution-formed and solid-state products, this is likely to be due to differences in the disordered solvent molecules within the channels as well as the exact stoichiometry, *i.e.* amount of DMSO incorporated.

In conclusion, we demonstrate a green synthetic strategy with the combination of mechanochemistry and solid-state photodimerisation. The formation, by grinding, of co-crystals of appropriate structure to enable sterero- and regio-control to take place, results in successful synthesis of **tpcb**. Thereafter, the additional solid-state grinding of the irradiated mixture with DMSO enables the formation of the desired channel structure. **bta**, interestingly, acts both as the supramolecular template for **bpe** alignment, and as the cavity building block. Overall, the process described illustrates how mechanochemistry in conjunction with UV irradiation can provide an effective eco-friendly route to novel porous supramolecular solids.

Experimental

All chemicals were used as purchased from Aldrich and without further purification. The PXRD patterns were recorded at room temperature using a Philips X'Pert diffractometer with Cu Kα radiation (λ = 1.5418 Å; 40 kV, 40 mA). The PXRD patterns were obtained using a 2-theta range of 5.00 to 50.00 degrees. ^{1}H NMR was performed on a Bruker DPX-400 spectrometer operating at 400 MHz. Samples were prepared in d_6-DMSO, and analysed at 300 K.

Ground samples were prepared using a *Retsch MM 200* Mixer Mill, with oscillation frequency of 15 Hz. The mixture of **bpe** and **bta** (molar ratio 2 : 1) used in grinding was *ca.* 300 mg in weight. All solvents introduced into the grinding mixtures are *ca.* 0.05 ml (2 drops from pipette) in scale and the solvents have been evaporated at room temperature before the PXRD analysis. UV irradiation was carried out using a TM G8T5 UV lamp (λ = 366 nm).

Acknowledgements

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New ionic liquids containing an appended hydroxyl functionality from the atom-efficient, one-pot reaction of 1-methylimidazole and acid with propylene oxide

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New ionic liquids containing (2-hydroxypropyl)-functionalized imidazolium cations have been synthesized by the atom-efficient, room temperature reaction of 1-methylimidazole with acid and propylene oxide; the acid providing the anionic component of the resultant ionic liquids. The incorporation of the secondary hydroxyl-functionality in the cation causes some interesting modifications to the behavior of these ionic liquids, increasing hydrophilicity and resulting in the unprecedented formation of liquid–liquid biphases with acetone. The single crystal structure of 1-(2-hydroxypropyl)-3-methylimidazolium tetraphenylborate, prepared by metathesis of the corresponding chloride-containing ionic liquid, has also been determined.

Introduction

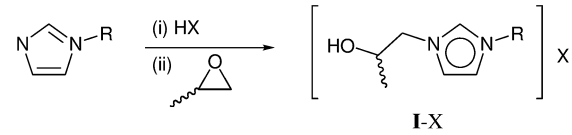
Ionic Liquid (IL) research is currently undergoing an unprecedented explosion of interest; the number of papers and patents currently being published reflects both academic and industrial interest in using ILs in diverse areas ranging from synthetic and catalytic chemistry to biotechnology, electrochemistry, and material science.[1,2] This growth can be traced to the development of new ILs in the mid 1990s that did not require the use of anhydrous handling conditions.[3] However, limitations to the efficient preparation of ionic liquids still hampers utilization and ensures that current commercial ILs have a large price premium.

Most synthetic procedures to prepare ILs feature initial alkylation of *N*-containing organic bases (amines and *N*-heterocycles) with alkylhalides, followed by metathesis to exchange the anion. An important factor to address for effective utilization of ILs as solvents within green chemistry is to provide clean, efficient syntheses of the ILs themselves, so that additional waste is not introduced into the overall process. Clean routes to afford quaternized cations and introduction of the desired anion for IL formation without salt-forming metatheses have been achieved using alternative alkylating agents[3d,4,5] or by one-pot syntheses of IL salts,[6] but have not displaced the conventional methodologies.

The properties of ILs can be varied by changing the nature of the anions, the cation, or both. A wide range of cation families have been investigated including *N*-alkylpyridinium, *N*,*N*-dialkylimidazolium, alkylammonium, phosphonium, and saturated cyclic quaternary ammonium salts.[1] In addition to changing the core, charge-carrying region of the cation, modifications to the periphery of the cation can be made to control rheological and chemical properties, or to introduce functionality, for example to enable CO_2 sequestration,[7] or metal complexation and/or extraction.[8] We have recently described Hg^{2+} partitioning to a bis-imidazolium system linked *via* polyethylene glycol units.[9] Introduction of ether and thioether groups into ILs has been reported to impart antistatic and biocidal properties,[10] and to increase solubility of $HgCl_2$ and $LnCl_3$,[11] and nucleosides.[12]

ILs derived from naturally occurring choline chloride (vitamin B4)[13] have been described and these ILs contain an alcohol function close to the charge-carrying core of the cation. The feasibility of stabilizing enzymatic catalysts, other than lipases, in ILs (and other organo-active systems) by providing a more water-like, or at least hydroxyl-rich microenvironment, without losing the potential solvent properties and benefits of an IL system,[14] make the introduction of hydroxyl-groups into other ILs[11] an attractive avenue of research.

We present here, the synthesis and characterization of new imidazolium-based ILs containing a secondary alcoholic functional group appended to the alkyl chain of the cation (Fig. 1).



I-X

Fig. 1 Generalized synthesis of ILs containing 1-(2-hydroxypropyl)-3-methylimidazolium cations by reaction of 1-methylimidazole with acid and propylene oxide (R = CH_3; X = Cl, [NO_3], [PF_6], [NTf_2]).

The ILs, 1-(2-hydroxypropyl)-3-methylimidazolium salts, are prepared by the atom-efficient coupling of the epoxide, propylene oxide, with an *N*-protonated imidazolium salt,

Green Context

The remarkable level of research interest in ionic liquids and the range of their potential applications as VOC solvent replacements, catalytic solvents and electrochemical media, among other things, demands the synthesis of new ILs with different properties. Here the known ring opening reaction of an epoxide with a base is exploited so as to make novel hydroxyalkyl ILs. These liquids have interesting properties including high hydrophilicity and a potential for enzyme stabilisation. ***JHC***

prepared *in situ* from 1-methylimidazole and an acid. The choice of acid dictates the resultant anion of the IL prepared and so enables a range of ILs to be prepared with different anions in a clean, single-step process, without requiring further metathetical anion exchange steps.

Results and discussion

Synthesis, characterization, and physical properties

The reaction of imidazole with propylene oxide and with other oxides has been previously described.[15] The authors report efficient formation of 1-(2-hydroxypropyl)imidazole at room temperature after 17 h, but that for other substituted imidazoles or epoxides, poorer yields and more vigorous reaction conditions are required. 1-Vinylimidazole has been reacted with propylene oxide under acidic conditions to form monomers for subsequent polymerization,[16] however, the imidazolium intermediates were not isolated or characterized. Coupling reactions, most notably utilizing epichlorohydrin to immobilize imidazolium functions have also been widely reported for the preparation of ion-exchangers, dye-fixatives, and antistatic agents,[17] and it should be noted that imidazole is used as a catalyst for the curing of epoxy-resins.[18] Arnold and co-workers[19] have described silver and copper carbene complexes containing alkoxide functions, formed with a diimidazolium precursor prepared by treating 1-*tert*-butylimidazole with a functionalized epichlorohydrin. Coupling of *N*-alkylimidazoles with chiral styrene epoxide[20] and epoxycyclohexane[21] have also been reported under microwave conditions as precursors to crystalline imidazolium salts (prepared by subsequent methylation with methyl iodide) and carbene ligands for metal complexation. The application of the reaction of imidazole derivatives with epoxides to prepare characterized room temperature ionic liquids has not, to the best of our knowledge, previously been described.[22]

ILs were prepared by protonating 1-methylimidazole with the acids, HCl, H[NTf_2], HNO_3, HPF_6, followed by reaction with propylene oxide (Table 1). The reaction of 1-methylimidazole with the acids, HCl, HNO_3, HPF_6 followed by addition of 1 equivalent of propylene oxide in ethanol at room temperature resulted in the quantitative formation of the corresponding ILs (**I**-Cl, **I**-[NO_3], **I**-[PF_6]) containing the 1-(2-hydroxypropyl)-3-methylimidazolium cation, as monitored by ^{1}H NMR. When bis(trifluorosulfonyl)amide ($HNTf_2$) was used as the acid, reaction with one equivalent of propylene oxide resulted in incomplete reaction, but yielded quantitative conversion to the respective IL (**I**-[NTf_2]) when an excess (~2 equiv.) of propylene oxide was used.

When the coupling reaction was attempted using either more bulky alkylimidazole or epoxides (Table 1), reaction yields were significantly reduced. The reaction of 1-butylimidazole with one equivalent of propylene oxide resulted in mixed systems containing *ca*. 35–38% 1-(2-hydroxpropyl)-3-butylimidazolium cations, with the remainder protonated 1-butylimidazolium determined by ^{1}H NMR, similar to the reactions of propylene oxide with 1-methylimidazole/acid systems. Subsequent reaction with a further equivalent of propylene oxide resulted in complete conversion from 1-butylimidazole to 1-(2-hydroxypropyl)-3-butylimidazolium chloride (**II**-Cl), as a colorless liquid.

Reactions were monitored by ^{1}H NMR spectroscopy of the crude reaction mixtures. None of the remaining systems screened (**III–V**) resulted in sufficient conversion of the initial imidazole to be effective for the synthesis of ILs as bulk solvents for further studies under the reaction conditions used (Table I), and the products were not isolated. The combinations screened included 1,2-dimethylimidazole and 1-decyl-2-methylimidazole with propylene epoxide, and 1-methylimidazole with 1,2-epoxydodecane; all using HCl and the conditions described in the experimental section for preparation of **I**-Cl.

In the original work of Cooper and Wilson,[15] the lower reactivity of C-substituted imidazoles with propylene oxide was observed and ascribed to steric factors reducing reaction rates. It is also possible that differences in the basicity of the initially formed imidazolium salts may also be a factor, as has been observed in the synthesis of alkylimidazoles.[23] Similarly, N-(2-hydroxypropyl)pyridinium cations have been reported from the direct alkylation of pyridine with 2-hydroxychloropropane, whereas reaction of pyridine with propylene oxide resulted in only polymer formation.[24] Further investigation and reaction optimization may lead to improvements, particularly using pressure systems to enable higher temperature reactions,[20] or by using microwave activation.[15]

For the IL systems **I** and **II**, removal of the reaction solvents (ethanol and water) and excess propylene oxide allowed isolation of the ILs as clear, colorless liquids which were characterized by proton and carbon NMR and by UV/Vis spectroscopy. Water content was determined for dried (and water-equilibrated **I**-[NTf_2]) samples by Karl–Fisher titration; melting and glass transitions were measured by DSC; and the thermal stability was measured dynamically using TGA under N_2. Results are tabulated in Table 2.

Treating a solution of **I**-Cl in water with aqueous $LiNTf_2$ resulted in formation of **I**-[NTf_2] indirectly, as a dense, immiscible phase, using the conventional metathesis route for preparation of [NTf_2]-containing ILs. The properties of the IL prepared this way were indistinguishable to those when prepared using the single stage, direct method, demonstrating the facility for efficient one-step formation of ILs. Treating an aqueous solution of **I**-Cl with aqueous HPF_6 resulted in the formation of a monophasic solution which was not characterized further, but directly indicates that **I**-[PF_6] is water soluble, and can not be prepared by metathesis in water using the procedures commonly employed for other 1,3-dialkylimidazolium hexafluorophosphate salts. Methathesis of **I**-Cl with sodium tetraphenylborate in water resulted in the precipitation of **I**-[BPh_4] as a white powder, which was recrystallized from ethanol–water to obtain crystals suitable for structure determination. The tetraphenylborate salt, characteristically, is much higher melting than the corresponding salts with other anions

Table 1 Reaction compositions investigated

	Base	Acid	Epoxide[a]	Yield (%)[b]
I-Cl	1-methylimidazole	HCl	PO	> 99
I-[NO_3]	1-methylimidazole	HNO_3	PO	> 95
I-[PF_6]	1-methylimidazole	HPF_6	PO	> 95
I-[NTf_2]	1-methylimidazole	$HNTf_2$	PO	> 99
II-Cl	1-butylimidazole	HCl	PO	> 95
III	1-methylimidazole	HCl	1,2-epoxy dodecane	< 8
IV	1,2-dimethyl-imidazole	HCl	PO	< 5
V	1-decyl-2-methylimidazole	HCl	PO	< 3

[a] PO is propylene oxide. [b] Product : reagent ratio estimated from ^{1}H NMR of crude reaction mixtures after evaporation of solvents.

Table 2 1-(2-Hydroxypropyl)-3-methylimidazolium salts isolated and their properties

IL	T_g/°C[a]	Mp/°C[a]	T_{dec}/°C[b]	Water content/wt%	Density/ g mL^{-1}	Viscocity/ cPs[c]
I-Cl	−68.9	—	300	5.29[d]	1.15	1856
I-[PF_6]	−88.4	—	325	2.22	1.11	319
I-[NTf_2]	−67.6	—	425	0.95 6.11[e]	1.57	342
I-[NO_3]	−79.3	—	320	0.11	1.17	502
II-Cl	—	136.5[f]	~250	—	—	—

[a] Glass transition (T_g) and melting point (Mp) from onset position were determined by DSC from the first heating cycle, after initially cooling samples to −150 °C. [b] Decomposition temperatures (T_{dec}) were determined by TGA, heating at 10 °C min^{-1} under nitrogen. [c] Measured at 25 °C. [d] Water content, after moderate drying, corresponds to 1:0.58 IL:H_2O. [e] After equilibration with an aqueous phase, water content corresponds to 1:1.57 IL:H_2O. [f] Enthalpy of melting, ΔH_m = 173 kJ mol^{-1}.

used to prepare ILs, and has a large enthalpy of melting. The structure of **I**-[BPh_4], described below, shows formation of racemic crystals containing both cation isomers as a hydrogen-bonded dimer.

All the ILs prepared (Table 2) were dried under high vacuum to yield moderately viscous fluids that varied in water content from 0.11 wt% (**I**-[NO_3]) to 5.29 wt% (**I**-Cl), which, interestingly, are the two with the most hydrophilic anions. The dramatic reduction of IL viscosity in the presence of water, or other low viscosity contaminants has been described by Seddon and co-workers.[25] However, for these systems, the IL with greatest water content (**I**-Cl) also had the highest viscosity. This feature may indicate that the ILs exhibit local structuring interactions and 'fragility'[26] in the liquid state, which might be anticipated with the introduction of the hydroxyl-group in the cation that has both hydrogen-bond donor and acceptor capabilities.

I-[PF_6] was found to contain 2.22 wt% water when dried and the low viscosity measured could be ascribed to the relatively high water content. Since **I**-[PF_6] proved to be totally miscible with water and hexafluorophosphate-containing ILs can have known problems with hydrolytic stability,[27] this system was not dried further. The viscosity of the ILs decreased rapidly as the ILs were heated above room temperature, and qualitatively, the change appeared to be more rapid than for conventional 1,3-dialkylimidazolium ILs.

The thermal behavior of the ILs was examined visually and by DSC. None of the ILs displayed a freezing transition on cooling to −15 °C in bulk, or to −150 °C (by DSC). In the bulk state, cooling overnight to −15 °C produced viscous non-crystalline materials. A glass transition was observed by DSC, in each case in the region −70 to −90 °C on heating from −150 °C with a 5 °C min^{-1} gradient. Although lower melting points might be anticipated by comparison with either the corresponding 1-*n*-butyl- and 1-*sec*-butyl-3-methylimidazolium analogs containing only carbon-substituents,[28] it should be noted that many ILs can be observed to significantly super-cool without crystallization, even when melting points, or even single crystal structures, established that the materials are solid at room temperature.[29]

The thermal decomposition temperatures of these ILs were determined using TGA, heating under an inert N_2 atmosphere at 10 °C min^{-1}. The thermal decomposition profiles are characteristic for ILs, the only mass loss below 300 °C was a small drop between 100–160 °C corresponding to removal of water and was consistent with the water-contents determined by Karl–Fisher titration. In each case, a subsequent single catastrophic weight loss is observed for decomposition of the IL on heating from 300–600 °C (Fig. 2). The stability of each IL is dependent on the anion present, **I**-Cl was the least stable (T_{dec} ~ 300 °C) whereas **I**-[NTf_2] was the most stable (T_{dec} ~ 425 °C). The relative stability of the ILs follows the order Cl^- < $[NO_3]^-$ < $[PF_6]^-$ < $[NTf_2]^-$, consistent with decomposition of the ILs *via* elimination of the imidazolium *N*-substituents, yielding volatile degradation products.

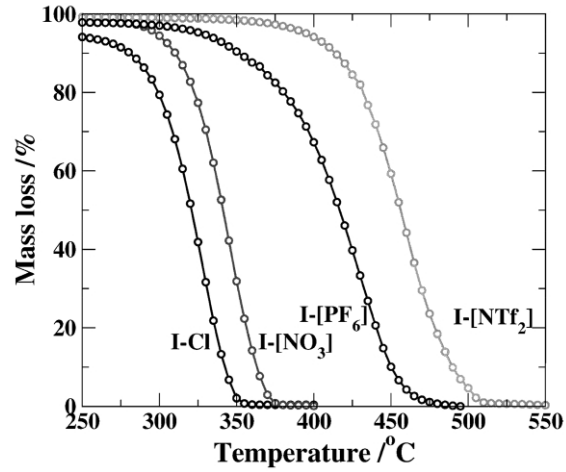


Fig. 2 Thermal decomposition profiles for the 1-(2-hydroxypropyl)-3-methylimidazolium ILs determined by TGA, heating under N_2 at 10 °C min^{-1}. The order of stability, Cl^- < $[NO_3]^-$ < $[PF_6]^-$ < $[NTf_2]^-$ is characteristic of ILs.[1]

Miscibility and liquid properties

As a result of addition of the hydroxyl-function to the cation, the ILs prepared here are significantly more hydrophilic than corresponding conventional 1,3-dialkylimidazolium systems. Both **I**-Cl and **I**-[NO_3] were hydroscopic, absorbing water when exposed to a moist atmosphere. Unusually, the hexafluorophosphate-containing IL, **I**-[PF_6], was also water soluble. The enhancement of water-miscibility by addition of the hydroxyl group can clearly be seen. Whereas some organic hexafluorophosphate salts with small cations (for example, ammonium, and dimethylimidazolium) are water miscible, most IL examples are only sparingly miscible with water, and are the principle examples of 'hydrophobic' ILs.

I-[NTf_2] formed a biphase when contacted with water, in common with other [NTf_2]-containing ILs. However, the hydrophilicity of **I**-[NTf_2] in comparison with the corresponding 1,3-dialkylimidazolium salts, is much higher. After drying *in vacuo*, **I**-[NTf_2] was determined to contain 0.95 wt% water (0.22 mole equivalents), however after contacting with water, the equilibrium water content was 6.11 wt% (1.5 mole equivalents), significantly higher than the water contents reported for corresponding [NTf_2]-ILs.[3d] Similarly, the chloride salt **I**-Cl retained a relatively high weight percent of water (as determined by Karl–Fisher titration), even after drying under high vacuum. After moderate, but not exhaustive drying under vacuum, the water content of **I**-Cl was 5.29 wt% water. This value corresponds to ~0.5 mole of water, and it could be considered that this is bound water, coordinated in the IL as a hemihydrate. Exhaustive drying of a small sample, with heating *in vacuo* to 150 °C accomplished dehydration of the IL, yielding the anhydrous chloride salt as a hydroscopic liquid.

The miscibility of the hydrophilic ILs, **I**-Cl and **I**-[NO_3] was determined with a range of molecular solvents. The ILs were

found to be completely miscible with water, DMSO, and acetonitrile, and formed biphasic systems with benzene, hexane, and diethylether. Unusually, both **I**-Cl and **I**-[NO_3] formed biphases with acetone. This appears to be unprecedented: from our observation and the literature;[30] all room temperature ILs reported have been completely miscible with acetone, although certain solid, crystalline organic chloride salts (including some imidazolium systems) are insoluble or sparingly soluble in acetone. It is not clear how the addition of the hydroxyl functionality helps induce formation of a biphase with acetone (a polar, hydrophilic liquid), and further studies are necessary to understand and exploit this phenomenon.

X-Ray crystallographic studies

The crystal structure of 1-(2-hydroxypropyl)-3-methylimidazolium tetraphenylborate (**I**-[BPh_4]) was determined.† The salt crystallizes as a hydrogen bonded dimer *via* a cation···cation hydrogen bonded core (Fig. 3, *left*) and cation···anion hydrogen bonded termini (Fig. 3, *right*).

The imidazolium cation has a characteristic planar conformation; all the ring C–C and C–N distances and angles are within the normal range for *N*,*N*′-dialkylimidazolium cations. The 2-hydroxypropyl substituent on N(1) is bent out of the plane of the heterocyclic ring, again a characteristic feature of alkylimidazolium crystal structures, with O1 projecting on the C(2) side of the ring, allowing both the C(8)–O lone-pair hydrogen-bond acceptor, and C(2)–H acidic hydrogen-bond donor sites to point in approximately the same direction.

I-[BPh_4] forms racemic crystals containing both *R*- and *S*-isomers of the cation in the unit cell. The two cations form a hydrogen-bonded dimer (Fig. 3, *left*), connected by two strong almost linear hydrogen bonds from the acidic imidazolium-ring C(2)-hydrogens to the oxygen atoms of the opposing cation (C2–H2A···O1a, 2.211(18) Å, 175.9(14)°). The hydrogen-bonding from O1 to the C(2)-hydrogen of the imidazolium rings occurs, even though the –OH group also has a good hydrogen-bond donor atom (H1). Hydrogen-bonding of the two enantiomeric cations results in formation of a racemic hydrogen-bonded cation dimer, through two C2–H2A···O1a interactions, which fixes the position of the hydroxypropyl chain.

Interestingly, the hydrogen of the hydroxyl-group (H1) does not participate in the cation–cation hydrogen bonding and is directed away from the cation-pair, projecting orthogonal to the plane of the imidazolium ring and pointing into a cleft within the tetraphenylborate anion (Fig. 3, *right*). This results in four close contacts from H1 to B, C16, C22, and C27 of the anion (O1A–H1A···X = 3.07(3) (B), 2.70(2), 2.64(3), and 2.55(3) Å, respectively). Each imidazolium ring also π–π stacks with a phenyl-ring associated with the second cation of the dimer, the closest contact being C2···C25a (3.371(3) Å). Weak, potential hydrogen bonding interactions between the C4 and C5 ring hydrogens and phenyl groups of neighboring dimers, serve to connect the dimers in chains along the *a* crystallographic axis.

The cation–cation structuring, observed in the crystal form may also be present in the liquid state for ILs containing the cation **I**. The directed hydroxyl-hydrogen (H1) would then be available to interact with anions, forming extended chains of the form –[CC]–A–[CC]–A– where [CC] corresponds to cation-pairs and A is the anion. Welton and co-workers[31] have demonstrated the interactions of water molecules with IL anions, and anion–water chains can be observed in the crystal structures of many organic salts.[27] Such structuring might account for our preliminary observations regarding the changing viscosity of these ILs with temperature, compared qualitatively with analogous dialkylimidazolium ILs.

Conclusions

The formation of ILs containing secondary alcohol functionalized imidazolium cations has been investigated. New imidazolium ILs were prepared by the reaction of propylene oxide with methylimidazole and acid (Fig. 1). The methodology is based on the established reactions of heterocyclic bases with epoxides,[20] and produces no waste other than reaction solvents (ethanol and water) and unreacted excess epoxide, all of which can be recovered. In addition, the reactions appear to be amenable to the use of a variety of acids, thus allowing a simple, atom-efficient room temperature synthesis of this class of ILs in which desired anions can be introduced without requiring subsequent metathesis steps. We have also demonstrated that the anion of these ILs can be exchanged using established metathetical routes, as illustrated by the conversion of **I**-Cl to **I**-[NTf_2] and to **I**-[BPh_4].

The ILs prepared here are all characteristically clean, and non-absorbing in the visible region, even without any additional treatment, which can be a significant factor for spectroscopic studies. The ILs are more hydrophilic that the corresponding systems with alkyl-functionalized cations, as anticipated by incorporation of the hydroxyl group, notably **I**-[PF_6] is completely miscible with water, in contrast to most ILs containing $[PF_6]^-$ anions. It is also worth pointing out that it should be possible to directly prepare chiral ILs using this procedure, utilizing the range of chiral epoxides that are becoming more readily available with recent advances in catalytic chiral expoxidation reactions.[32]

In these ILs, both hydrogen-bond donating and accepting positions (–O*H*, and –*O*H, respectively) have been introduced

† CCDC reference number 224058. See http://www.rsc.org/suppdata/gc/b3/b311717k/ for crystallographic data in .cif or other electronic format.

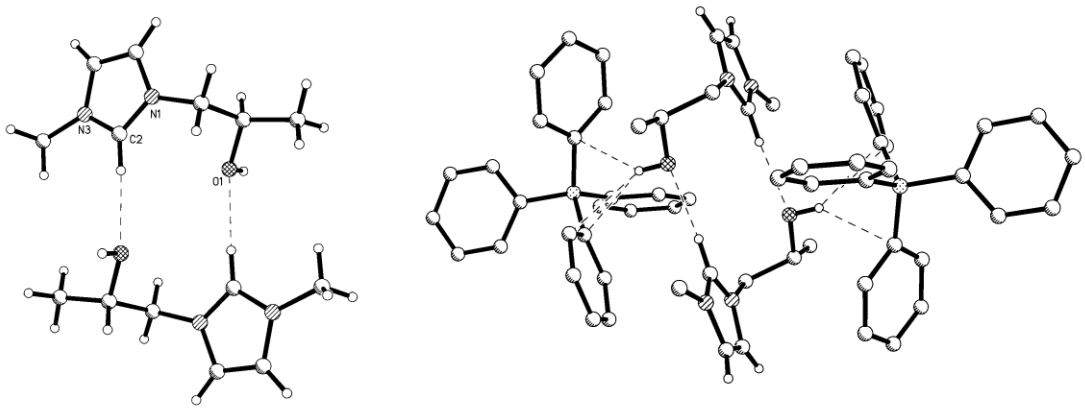


Fig. 3 The hydrogen-bonded dimer formed by *R*/*S*-pairs of the 1-(2-hydroxypropyl)-3-methylimidazolium cations (left) and hydrogen-bonding from the cation hydroxyl-group to the tetraphenylborate anions (right) in **I**-[BPh_4].

into the cationic portion, and a comparison with ether-functionalized ILs containing only hydrogen-bond acceptor sites could be informative. The hydrophilicity afforded by the secondary hydroxyl-group may be advantageous for stabilizing enzymatic catalyst systems in non-aqueous IL environments, and may also provide new applications in metal complexation and partitioning.

Experimental

All reagents were used as received. Bis(trifluoromethanesulfonyl)amide (neat), lithium bis(trifluoromethanesulfonyl)amide, and hexafluorophosphoric acid (66 wt% solution in water) were gifts from Rhodia (Cranbury, NJ), 3M (St. Paul, MN), and Ozark Fluorine Specialties (Folcroft, PA), respectively. 1-Methylimidazole and propylene oxide were purchased from Aldrich (St. Louis, MO). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM360 spectrometer in DMSO-d_6. Peak positions are reported relative to DMSO-d_6 (δ_H = 2.50 ppm, δ_C = 40.45 ppm). Melting points and glass transition temperatures were determined by differential scanning calorimetry (TA 2620 DSC equipped with cryostat cooling, 5–20 mg samples, 5 °C min^{-1} heating and cooling rates). Thermal decomposition profiles were collected by thermogravimetric analysis (TA 2950 TGA, 10 °C min^{-1} heating rate under nitrogen).

Caution: propylene oxide is a volatile, flammable, carcinogenic liquid (bp 34 °C) that can react violently with both strong acids and bases. In all studies, care was taken to ensure that the alkylimidazole bases and acid reagents were thoroughly reacted and neutralized prior to introduction of the epoxide reagents into the reaction vessels. At all times, reaction temperatures were maintained at, or below 25 °C and the reactions were carried out in a well ventilated fumehood.

1-(2-Hydroxypropyl)-3-methylimidazolium chloride (I-Cl)

To a stirred solution of 1-methylimidazole (20 mL, 20.6 g, 0.25 mol) in ethanol (40 mL) at room temperature was carefully added concentrated hydrochloric acid (21 mL, 0.255 mol). *Caution: neutralization of base with a strong acid is highly exothermic.* After addition of acid, the reaction mixture was cooled to room temperature and propylene oxide (18 mL, 15 g, 0.26 mol) was added dropwise with stirring while maintaining the temperature at 25 °C. The reaction vessel was then sealed and stirred at room temperature for 24–48 h. The solvent was removed under reduced pressure with heating at 70 °C, followed by heating under high vacuum, to yield a colorless liquid that became more viscous upon extensive drying, but did not solidify. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.05 (3H, d, CH_3), 3.57 (2.2H, H_2O), 2.88 (3H, s, N–CH_3), 4.0 (2H, m), 4.26 (1H, dd, AA′B NCH_2CH(OH)–), 5.50 (1H, d, C(OH)), 7.74, 7.75 (2H, 2 × s, C(4,5)–H), 9.24 (1H, s, C(2)–H). ^{13}C (90.5 MHz, DMSO-d_6) 20.32 (CH_3), 35.83 (N–CH_3), 55.54 (N–CH_2), 64.88 (CH(OH)), 123.16 (C(4,5)), 137.00 (C(2)). MS: (EI+) m/z 141 [**I**$^+$, 100%], 126 [{**I**-CH_3}$^+$].

1-(2-Hydroxypropyl)-3-methylimidazolium bis(trifyl)amide (I-[NTf$_2$])

I-[NTf$_2$] was prepared using the same procedure as **I**-Cl using bis(trifluoromethanesulfonyl)amide (HNTf$_2$, 70 g, 0.25 mol). After reaction of the 1:1:1 mixture for 24 h, ^{1}H NMR indicated a mixture containing 3:1 product:starting material. A further aliquot of propylene oxide (10 mL, 0.14 mol) was added and stirred at room temperature for a further 24 h; evaporation of the solvent and excess propylene oxide yielded **I**-NTf$_2$ as a hydrophobic colorless liquid. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.10 (1H, d, J = 5.9 Hz, –CH_3), 3.86 (3H, s, N–CH_3), 3.95 (2H, m), 4.17 (1H, m) [AA′B, NCH_2CH(OH)–], 5.20 (1H, d, J = 3.6 Hz, C–OH), 7.62, 7.63 (2H, 2 × s, C(4,5)–H), 9.00, (1H, s, C(2)–H). ^{13}C NMR (90.5 MHz, DMSO-d_6) δ 20.26 (CH_3), 35.76 (N–CH_3), 55.89 (N–CH_2), 64.93 (CH(OH)), 119.69 (q, J_{C-F} = 343 Hz, CF_3), 123.21, 123.22 (C(4,5)), 137.07 (C(2)). MS: (EI+) m/z 141 [{**I**}$^+$, 100%], 123 [{**I**-H$_2$O}$^+$].

Preparation of **I**-[NTf$_2$] by metathesis from **I**-Cl. To a stirred solution of **I**-Cl in water was added a solution of LiNTf$_2$ in water, resulting in immediate biphase formation. The lower, IL phase was collected, washed with water, and dried under reduced pressure with heating at 70 °C to yield a colorless liquid. Analysis and appearance were identical to the product prepared by the direct method.

1-(2-Hydroxypropyl)-3-methylimidazolium hexafluorophosphate (I-[PF$_6$])

I-[PF$_6$] was prepared by reaction of 1-methylimidazole with HPF$_6$ (37 mL, 0.25 mol, 66 wt% solution in water) and propylene oxide in ethanol, following the procedure described for **I**-Cl. Removal of the volatile solvents under reduced pressure, followed by final drying *in vacuo* at 70 °C gave a colorless liquid. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.08 (3H, d, J = 5.5Hz, –CH_3), 3.83 (s, 3H, N–CH_3), 3.94 (2H, m), 4.17 (1H, m) [AA′B system, NCH_2CH(OH)–], 7.58, 5.59 (2H, 2 × s, C(4/5)–H), 8.92 (1H, s, C(2)–H). ^{13}C NMR (90.5 MHz, DMSO-d_6) δ 20.50 (–CH_3), 35.97 (N–CH_3), 56.03 (N–CH_2), 65.16 (CH(OH)), 123.36, 123.42 (C(4/5)), 137.11 (C(2)). MS: (EI+) m/z 140 [{**I**-1}$^+$], 123 [{**I**-H$_2$O}$^+$, 100%].

1-(2-Hydroxypropyl)-3-methylimidazolium nitrate (I-[NO$_3$])

I-[NO$_3$] was prepared by reaction of 1-methylimidazole (20 mL, 20.6 g, 0.25 mol) with conc. nitric acid (16.5 mL, 0.25 mol) and propylene oxide (30 mL, 24.9 g, 0.43 mol) in ethanol (40 mL), following the procedure described for **I**-Cl. Removal of the volatile solvents under reduced pressure, followed by final drying *in vacuo* at 70 °C gave a colorless liquid. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.07 (3H, d, J = 5.5 Hz, –CH_3), 3.85 (s, 3H, N–CH_3), 3.93 (2H, m), 4.20 (1H, m) [AA′B system, NCH_2CH(OH)–], 5.50 (1H, b, C–OH), 7.69 (2H, s, C(4/5)-H), 9.08 (1H, s, C(2)–H). ^{13}C NMR (90.5 MHz, DMSO-d_6) δ 20.31 (–CH_3), 35.66 (N–CH_3), 55.68 (N–CH_2), 64.80 (CH(OH)), 123.12, 123.19 (C(4/5)), 137.02 (C(2)). MS: (EI+) m/z 139 [{**I**-3}$^+$, 100%], 206 [{**I**-[NO$_3$]+3}$^+$].

1-(2-Hydroxypropyl)-3-methylimidazolium tetraphenylborate (I-[BPh$_4$])

Crystals of **I**-[BPh$_4$] were prepared by metathesis of **I**-Cl in water with sodium tetraphenylborate. The white, insoluble precipitate which formed was collected by filtration, air dried, and recrystallized from ethanol–water as large colorless blocks. Mp 138 °C. ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.08 (3H, d, J = 5.5 Hz, –CH_3), 3.82 (s, 3H, N–CH_3), 3.91 (2H, m), 4.14 (1H, m) [AA′B system, NCH_2CH(OH)–], 5.19 (1H, b, J = 4.3 Hz, C–OH), 6.80 (4H, t, γ-CH), 6.93 (8H, t, α-CH), 7.18 (8H, m, β-CH), 7.63 (2H, s, C(4/5)–H), 8.98 (1H, s, C(2)–H).

1-(2-Hydroxypropyl)-3-butylimidazolium chloride (II-Cl)

Reaction of 1-butylimidazole (52.9 g, 90 wt% in water, 0.25 mol), concentrated hydrochloric acid (21 mL, 0.255 mol), and propylene oxide (18 mL, 15 g, 0.26 mol) in ethanol, following

the procedure for **I**-Cl, resulted in a colorless liquid containing 3:2 product:starting material based on ^{1}H NMR. A further portion of propylene oxide (18 mL, 0.26 mol) was added to the crude reaction mixture and stirred at room temperature for 24 h and unreacted propylene oxide was removed under reduced pressure, and then *in vacuo* with heating at 70 °C to yield **II**as a colorless liquid. ^{1}H NMR (360 MHz, DMSO-d_6) δ 0.85 (3H, CH_3), 1.06 (3H, d, CH_3), 1.21 (m, 2H), 1.75 (m, 2H), 3.93 (2H, t), 4.3 (1H, dd), 4,20 (1H, dd), 4.27 (1H, dd), 5.52 (1H, d, CO*H*), 7.85 (2H, C(4,5)*H*), 9.50 (1H, C(2)*H*).

Crystal structure of I-[BPh]$_4$

Colorless, blocky crystals of **I**-[BPh$_4$] were obtained by recrystallization from ethanol–water. X-Ray diffraction data were collected on a Siemens CCD area detector-equipped diffractometer with Mo–Kα (λ = 0.71703 Å) radiation at −100 °C using a stream of nitrogen gas. The crystal structure was solved by direct methods using the SHELXTL software package. All non-hydrogen atoms were anisotropically refined and all hydrogen atoms were located using difference Fourier maps and were isotropically refined. *Crystal Data for* **I**-[BPh$_4$]: Formula $C_{31}H_{33}BN_2O$, M = 460.4, a = 10.771(3), b = 11.201(3), c = 11.612(4) Å, α = 96.211(5), β = 111.392(5), γ = 94.957(5)°, V = 1284.7(7) Å^3, T = 173 K, space group P1 (#2), Z = 2, μ(Mo–Kα) = 0.071 mm^{-1}, R_1 = 0.0403, wR_2 = 0.1097 [$I > 2\sigma(I)$].

Acknowledgements

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Preparation of dichlorophenylphosphine *via* Friedel–Crafts reaction in ionic liquids

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The Friedel–Crafts reaction of PCl_3 and benzene in [BuPy]Cl–$XAlCl_3$ ionic liquids (ILs) was investigated for clean synthesis of dichlorophenylphosphine (DCPP). A simple product isolation procedure was achieved, and the effect of ILs composition, reactant composition, reaction time and quantity of ILs on this reaction were studied. The [BuPy]Cl–$XAlCl_3$ rendered this reaction green characteristics. A catalytic mechanism was proposed as well.

1 Introduction

Dichlorophenylphosphine (DCPP) is a commercially important compound in organic synthesis and it is widely used in the preparation of flame-retardants, insecticides, stabilizers, plasticizers, and antioxidants. It is generally prepared from phosphorus trichloride and benzene *via* the Friedel–Crafts reaction using a stoichiometric amount of or excess anhydrous aluminium chloride as catalyst.[1–4] The main difficulty in this preparation is isolating the product which forms a rather stable complex with aluminium chloride.[5] The isolation methods for other Friedel–Crafts reaction products, that is hydrolyzing the reaction mixture with water followed by extraction of the product with organic solvents, are not suitable for DCPP, because it is readily reacted with water. According to the literature,[2,5,6] phosphorus oxychloride or pyridine can be added to form a more stable aluminium chloride, so the DCPP can be liberated and then recovered by extraction with petroleum ether. But there are considerable problems in these preparation procedures. The added $POCl_3$ or pyridine would form a large quantity of another solid or a highly viscous complex with aluminium, which is toxic and difficult to handle in the following extraction procedure. The non-reusable complexes would greatly contaminate the environment by themselves or after hydrolyzation with water. While in other literature[7,8] it has been shown that using an appropriate amount of water to break-down the DCPP–aluminium complex will decompose the product and reduce the yields, the contamination problem still exists. Therefore, there is a strong incentive to find clean synthesis and simple isolation procedures for the preparation of DCPP.

Recently, much attention[9–12] has been focused on ionic liquids (ILs) for their advantageous use in the Friedel–Crafts reactions. The designable ILs possess green characteristics such as the absence of volatile organic compounds (VOCs), they can be readily recycled, they have a profound effect on the activity and selectivity in reactions and, in some cases, facilitate the isolation of products. There are literature examples[13–16] reporting clean synthesis reactions and improved reaction characteristics of the Friedel–Crafts alkylation and acylation reactions in ILs. For example, Adams[17] and coworkers studied the Friedel–Crafts acylation of toluene, chlorobenzene and anisole with acetyl chloride in [EMIM]Cl–$XAlCl_3$ (EMIM = 1-ethyl-3-methylimidazolium cation) and obtained excellent regioselectivities. Up to now, no attention has been given to the Friedel–Crafts reaction characteristics of PCl_3 and benzene in ILs.

The purpose of the present work is to investigate the reaction characteristics of PCl_3 and benzene using an IL, [BuPy]Cl–$XAlCl_3$ (BuPy = N-butylpyridinium cation, X is the mole fraction of $AlCl_3$ in the [BuPy]Cl and $AlCl_3$ system), as catalyst (Scheme 1).

Scheme 1

The effect of acidity (different X values) and amount of the ILs, the effect of reaction time and reactant composition on this reaction were studied. The catalytic behavior of the recycled catalysts was investigated, and a mechanism of the catalytic reaction was proposed. In addition, a procedure for extracting the DCPP directly from the reaction medium was successfully achieved.

2 Results and discussion

2.1 Isolation of DCPP

In all cases, DCPP was extracted with petroleum ether directly from the reaction mixture, and yields ranging from 56.2 to 68.4% (based on benzene) were obtained. This isolation method is different to the classical ones. In classical reactions using $AlCl_3$ as catalyst, the direct extraction of the DCPP usually produces yields below 20–25%, and often below 10%.[5] The methods adopted to break-down the aluminium complex followed by extraction with petroleum ether could improve the yields, but make the catalyst non-reusable. The successful isolation of DCPP using a direct extraction method indicated that most of the product was not in the complex form when the

Green Context

The Friedel–Crafts reaction is well documented as being a dirty reaction which needs improvement. Its use in the synthesis of arylchlorophosphines is particularly difficult due to the hydrolytic lability of the products. Here, ionic liquids have been used as carriers for aluminium chloride, and the product can be isolated in very good yields from the reaction mixture. ***DJM***

reaction was carried out in ILs. Therefore, extraction of the product would not destroy the catalyst, making it recyclable.

2.2 Catalytic activity of [BuPy]Cl–$XAlCl_3$ ionic liquids

Reaction cases using varied amounts of ILs with different ILs compositions (different X value in [BuPy]Cl–$XAlCl_3$ ionic liquids) were carried out to investigate the catalytic activity of [BuPy]Cl–$XAlCl_3$ ionic liquids in the Friedel–Crafts reaction of PCl_3 and benzene, and the results are summarized in Table 1.

Table 1 Catalytic activity of [BuPy]Cl–$XAlCl_3$ ILs

X	PCl_3 : benzene : ILs/mole ratio	Yield (%)
0.44	3 : 1 : 1	0.1
0.50	3 : 1 : 1	3.5
0.60	3 : 1 : 1	43.7
0.60	3 : 1 : 1.5	53.2
0.60	3 : 1 : 2	64.4
0.67	3 : 1 : 1	55.6
0.67	3 : 1 : 1.5	61.1
0.67	3 : 1 : 2	64.6
0.71	3 : 1 : 1	57.3
0.71	3 : 1 : 1.5	60.2
0.71	3 : 1 : 2	68.4
0.60	30 : 10 : 1	40.1
0.67	30 : 10 : 1	44.7
0.71	30 : 10 : 1	54.5

Reactions were carried with refluxing for 8 h.

The acidic (X > 0.5) [BuPy]Cl–$XAlCl_3$ ILs showed fair catalytic activity in the Friedel–Crafts reaction of PCl_3 and benzene, and the catalytic activity increased as their acidity increased. In contrast, the basic (X = 0.4) and neutral (X = 0.50) [BuPy]Cl–$XAlCl_3$ ILs showed nearly no catalytic activity. These results were in agreement with those discovered in other ILs catalyzed Friedel–Crafts reactions.[13] Considering the Lewis acid in ILs, we can imagine that it is the Lewis acid $Al_2Cl_7^-$ that plays an important role in the catalytic activity in acidic ILs, while in basic and neutral ILs the $AlCl_4^-$ anion is unlikely to catalyze the reaction. The cases with low yields of 0.1 and 3.5% could be attributed to the trace equivalent ($AlCl_4^-$ and $Al_2Cl_7^-$)[18] in basic or neutral [BuPy]Cl–$XAlCl_3$ ILs.

$$2AlCl_4^- \rightleftharpoons Al_2Cl_7^- + Cl^-$$

With the same acidic ILs, using a large amount of ILs is favorable to improve the yields. The most interesting result in these cases is that the ILs could be used in catalytic quantity. Thus a yield of 54.5% was obtained in the case with a 30 : 10 : 1 molar ratio of PCl_3 : benzene : ILs.

2.3 Effects of reactant composition and reaction time

The effects of reactant composition and reaction time on the Friedel–Crafts reaction of PCl_3 and benzene were investigated.

We found from Table 2 that the cases using excess PCl_3 produced higher yields than those with a lower mole fraction of PCl_3. With the identified reaction mixtures, the reactions performed over a longer time were likely to give higher yields. With a catalytic quantity of ILs, the mole ratio of PCl_3 : benzene : [BuPy]Cl–$0.71AlCl_3$ is 30 : 10 : 1, and when the reaction time is 16 h a yield of 63.1% is obtained, while in 8 h the yield is 54.5%. We also found that if a reaction was carried out over too long a time, the yield would decrease after reaching its highest value. This means that preferred reaction times for the reactions exist, and that longer than that time is likely to add the opportunity for the side reaction to take place. Starting from the

Table 2 Effects of reactant composition and reaction time

PCl_3 : benzene : ILs/ mole ratio	Reaction time/h	Yield (%)
3 : 1 : 1	4	43.2
3 : 1 : 1	8	52.3
3 : 1 : 1	16	51.6
1 : 1 : 1	4	40.1
1 : 1 : 1	8	44.5
1 : 1 : 1	16	47.1
1 : 3 : 3	4	46.2
1 : 3 : 3	8	40.9
1 : 3 : 3	16	40.1
30 : 10 : 1	8	54.5
30 : 10 : 1	16	63.1
30 : 10 : 1	24	64.2
30 : 10 : 1	32	60.4

[a]ILs: [BuPy]Cl-$0.71AlCl_3$

reaction residue, we obtained diphenylphosphinic acid which indicated that the by-product is diphenylchlorophosphine.[3,19] An excess amount of PCl_3 would reduce the potential side reaction and thus is favorable for a higher yield. However we didn't get the by-product from the extract, which indicated that the by-product was in the ILs. We can't determine if it is insolvable in petroleum ether or if it is in the complex form with aluminium in the ILs. The formation of diphenylchlorophosphine will consume DCPP and reduce the catalytic activity of ILs thus affecting the yields and catalytic character of the reaction. Further study of the side reaction is continuing in our laboratory.

2.4 Reusable character of ILs

Part of the isolated ILs was used directly in the followed runs to investigate their reusable characteristics. From Table 3 it can be

Table 3 Reusable characteristics of ILs

PCl_3 : benzene : ILs/mole ratio	Run	Reaction time/h	Yield (%)
3 : 1 : 1	1	8	52.3
3 : 1 : 1	2	8	50.6
3 : 1 : 1	3	16	50.1
3 : 1 : 1	4	16	43.2
30 : 10 : 1	1	16	63.1
30 : 10 : 1	2	16	62.0
30 : 10 : 1	3	16	56.3
30 : 10 : 1	4	16	55.1

seen that the ILs were recyclable. The catalytic activity showed a slight decrease in the following three runs. However we still got a yield of 55.1% using recycled [BuPy]Cl–$0.71AlCl_3$ ionic liquids in the fourth run in 16 h, with a mole ratio of PCl_3 : benzene : ILs equal to 30 : 10 : 1.

2.5 Mechanism

The [BuPy]Cl–$XAlCl_3$ ionic liquids could be used as both solvent and catalyst for the Friedel–Crafts reaction of PCl_3 and benzene. The product is readily extracted with petroleum ether, which means that the product was not in the complex form with the aluminium as in classical reactions. A small amount of the ILs can catalyze the reactions to a yield of about 60% instead of the stoichiometric amount of or excess $AlCl_3$ described in literature methods. These results suggested that the reaction mechanism for the Friedel–Crafts reaction of PCl_3 and benzene of classical reactions needs to be modified to explain the

reaction in ILs. We propose the following mechanism for the Friedel–Crafts reaction in [BuPy]Cl–$XAlCl_3$ ILs.[13]

$$PCl_3 + Al_2Cl_7^- \rightarrow Cl_2P^+ + 2AlCl_4^- \quad (1)$$

$$Cl_2P^+ + Ph\text{–}H \rightleftharpoons H\text{–}Ph^+\text{–}PCl_2 \quad (2)$$

$$H\text{–}Ph^+\text{–}PCl_2 + AlCl_4^- \rightleftharpoons Ph\text{–}PCl_2 + HCl + AlCl_3 \quad (3)$$

$$AlCl_3 + AlCl_4^- \rightarrow Al_2Cl_7^- \quad (4)$$

We believe that in the first step there is an intermediate complex of PCl_3 and $Al_2Cl_7^-$, which decomposed quickly to dichlorophospinium and $AlCl_4^-$. The first and fourth steps are very rapid, and there is a rate-determining step in step 2 and step 3.

3 Conclusion

The Friedel–Crafts reaction of PCl_3 and benzene was successfully carried out in [BuPy]Cl–$XAlCl_3$ ionic liquids. Compared with classical methods to prepare DCPP, the reaction using [BuPy]Cl–$XAlCl_3$ ionic liquids as catalyst exhibited simple product isolation procedure, less and reusable catalyst consumption, which will contribute to the clean synthesis of DCPP. The reaction phenomenon means that identification of a new mechanism is needed to discover the initial characteristics of the Friedel–Crafts reaction of phosphorustrichloride and aromatic compounds in ILs. Though the yields in the present experiments are satisfying, they are relatively low for industrial synthesis, therefore, further study and other ILs systems should be investigated to promote the reaction.

4 Experimental

N-Butypyridinium chloride ([BuPy]Cl), aluminium trichloride, phosphorus chloride benzene and petroleum ether (60–90 °C) were all from VAS Chemical Reagent Corporation Ltd. in Beijing.

4.1 Instrumental analysis and measurements

Melting points were obtained from an X4 Micromelting point meter and the temperature was uncorrected. The C, H elemental analysis was performed on a Yanaco CHN FOER MT-3 element analyzer. IR spectra (FTIR) were recorded on a Perkin-Elmer 2000 FTIR spectrometer using KBr pellet. ^1H NMR spectra were recorded with a Varian Unity 200 MHz spectrometer with $CDCl_3$ as solvent. MS spectra were obtained on a HP-5989 mass spectrometer.

4.2 Preparation of ILs [BuPy]Cl–$XAlCl_3$ (X = 0.67)

In a round bottom flask equipped with a magnetic stirrer and a gas inlet valve, 26.67 g (0.2 mol) anhydrous $AlCl_3$ was slowly added to 17.15 g (0.1 mol) N-butylpyridinium chloride. The mixture was left stirring for 3 hours to ensure complete reaction.

Other compositions of [BuPy]Cl–$XAlCl_3$ (X = 0.50, 0.60, 0.71) were prepared according to the above procedure, with appropriate amounts of $AlCl_3$ and N-butylpyridinium chloride. (0.1 mol $AlCl_3$ and 0.1 mol [BuPy]Cl for X = 0.5, 0.15 mol $AlCl_3$ and 0.1 mol [BuPy]Cl for X = 0.60, 0.25 mol $AlCl_3$ and 0.1 mol [BuPy]Cl for X = 0.71).

4.3 General Friedel–Crafts reaction procedure

In a round bottom four necked flask equipped with stirrer, condenser and a gas inlet valve, the designed amount of PCl_3 and benzene were added to a weighed quantity of [BuPy]Cl–$XAlCl_3$. The mixture was heated and kept refluxing for the designed hours. Then the mixture was cooled to room temperature, extracted with 100 mL petroleum ether thrice and the above layers were combined. The ionic liquids layer was separated and saved for another reaction or preparation of diphenylphosphinic acid. The low boiling liquids in the organic layer, mostly petroleum ether, phosphorus trichloride, and benzene were removed by distillation at atmospheric pressure, followed by distillation at a slightly reduced pressure (6.67 KPa) below 90 °C. The DCPP was distilled under vacuum with boiling point 92–94 °C/1.56 KPa. (literature 90–92 °C/1.33 KPa,[20] 68–70 °C/0.133 KPa,[20] 94 °C/1.60 KPa[21]) density d_{30} 1.3576–1.3682 (literature, d_{25} 1.327 g mL^{-1},[20] $d_{30.9}$ 1.3567 g mL^{-1}[22]), viscosity η_{30} 3.01 mPa s (literature $\eta_{29.45}$ 2.99 mPa s[22]), refraction index n_D^{25} 1.5910–1.5914 (literature n_D^{25} 1.5912[20]), gas chromatographic analysis (GC-14C gas chromatograph) showed that the purity of DCPP was above 96.5%.

4.4 General procedure for preparation of diphenylphosphinic acid

The brown ILs layer obtained in the previous procedure was decomposed cautiously by adding it in small portions to an appropriate amount of dilute hydrochloric acid and ice in an open beaker. The reaction was vigorous and exothermic. A yellow gummy substance existed in the beaker at the end of the addition. The liquid was decanted, extracted with 150 mL benzene thrice, and the organic layers were collected. 100 mL warm benzene was added to dissolve the gummy substance, and combined with the above organic layer. The organic layer was washed by 100 mL 0.1 mol L^{-1} and 0.05 mol L^{-1} hydrochloric acid respectively, then washed by 100 mL thrice and left for 2 days. The organic layer was transferred to a flask, and 200 mL 0.1 mol L^{-1} sodium hydrogen chloride was added. The mixture was refluxed with stirring for 1 h, and then cooled to room temperature. The sodium hydroxide extract was separated and acidified with 0.1 mol L^{-1} hydrochloric acid to get white solid diphenylphosphinic acid which was washed with water and dried. mp 192 ~ 194 °C. Elemental analysis (%, calculated): C 66.06 (59.94), H 5.08 (5.03). IR (KBr): 2754 (P–OH), 1603, 1430 (Ar–P), 1150 (P=O) cm^{-1}. ^1H NMR (200 MHz, ($CDCl_3$ 200 MHz): δ 13.42 (1H, s, P–OH), 7.62 to 8.14 (5H, m, Ar–H), MS (EI): 217 (M^+-1).

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