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Volume 7 | Number 4 | April 2005 | Pages 169–240

ISSN 1463-9262

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Cover

Different stages in the production of textiles made from natural cellulose fibres extracted from cornhusks. The process has been carried out for the first time at the University of Nebraska-Lincoln, USA.

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CHEMICAL TECHNOLOGY

Chemical Technology

April 2005/Volume 2/Issue 4

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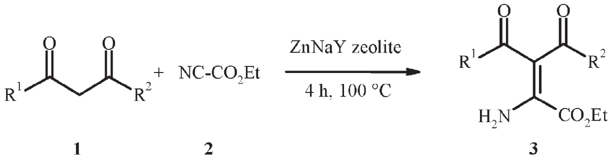

View Online

Downloaded on 02 November 2010
Published on 24 March 2005 on http://pubs.rsc.org | doi:10.1039/B503485J

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

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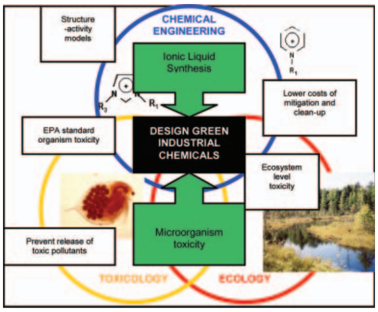
Toxicity and antimicrobial activity of imidazolium and pyridinium ionic liquids

Kathryn M. Docherty* and Charles F. Kulpa, Jr.

This research examines the toxicity and antimicrobial activity of imidazolium and pyridinium ionic liquids. It provides information for future cross-disciplinary studies to test IL toxicity, develop models and create green solvents.



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Narendra Reddy and Yiqi Yang*

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Jianji Wang,* Yuanchao Pei, Yang Zhao and Zhiguo Hu

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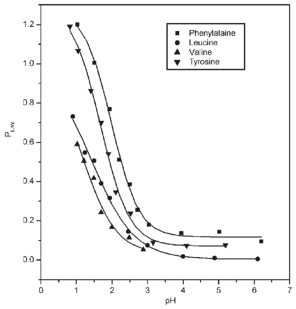

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Gadolinium triflate immobilized in imidazolium based ionic liquids: a recyclable catalyst and green solvent for acetylation of alcohols and amines

Ramesh Alleti, Woon Su Oh, Meher Perambuduru, Zahra Afrasiabi, Ekkehard Sinn and V. Prakash Reddy*

Gadolinium triflate immobilized in imidazolium based room temperature ionic liquids (RTILs) is a recyclable and green catalyst for acetylation of a variety of alcohols, phenols and amines.

$$\text{R-XH} + Ac_2O \xrightarrow[\text{[bmim][BF}_4\text{], RT}]{Gd(OTf)_3\ (0.2 - 0.5\ \text{mol}\ \%)} \text{R-XAc}$$

X = O, NH

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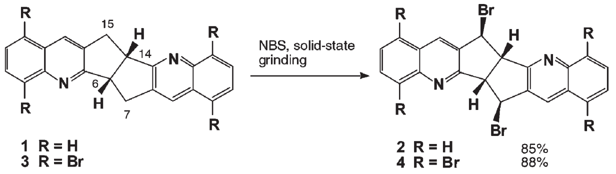

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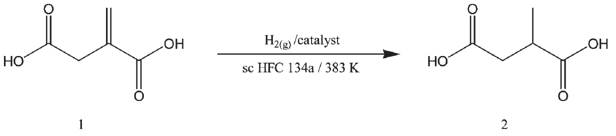

Solubility of unsaturated carboxylic acids in supercritical 1,1,1,2-tetrafluoroethane (HFC 134a) and a methodology for the separation of ternary mixtures

Andrew P. Abbott,* Wayne Eltringham, Eric G. Hope and Mazin Nicola

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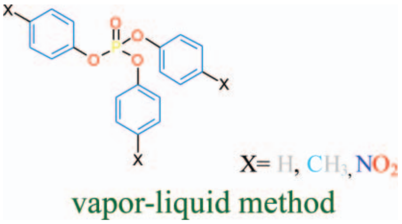

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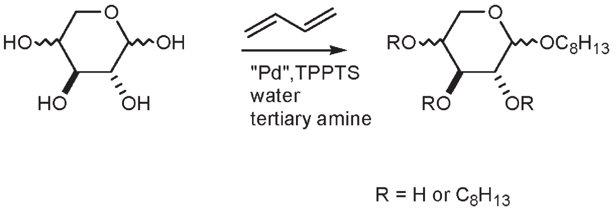

Telomerization of butadiene with pentoses in water: selective etherifications

Boris Estrine, Sandrine Bouquillon, Françoise Hénin* and Jacques Muzart

The telomerization of butadiene with pentoses carried out in water led to a selective mono or bis-etherification of the sugar, depending on the tertiary amine used as mediator. This constitutes an economic direct access to different classes of surfactant molecules, starting from this renewable feedstock.

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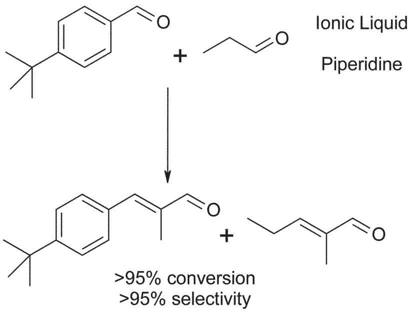
Synthesis of 3-(4-*tert*-butylphenyl)-2-propen-1-one, a precursor to Lilial®, *via* an aldol condensation in an ionic liquid

Paul N. Davey, Stewart A. Forsyth,
H. Q. Nimal Gunaratne, Christopher Hardacre,*
Angela McKeown, S. E. Jane McMath, David W. Rooney
and Kenneth R. Seddon

Aldol condensations have an inherent selectivity issue in that both cross aldol and self aldol reactions can occur. By using ionic liquids, the desired cross aldol condensation between 4-*t*-butylbenzaldehyde and propanal is promoted.



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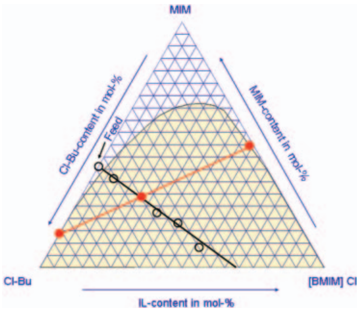
Kinetics of single- and two-phase synthesis of the ionic liquid 1-butyl-3-methylimidazolium chloride

Alexandra Großе Böwing and Andreas Jess*

[BMIM]Cl-synthesis was investigated for the neat two-phase and single-phase mode (solvent). The kinetic and thermodynamic data can be used for synthesis scale-up, preferably in a continuous tubular reactor.



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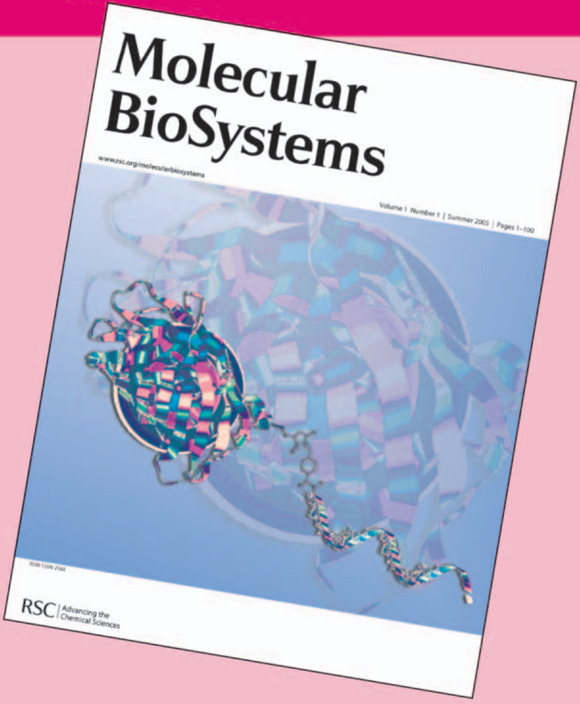
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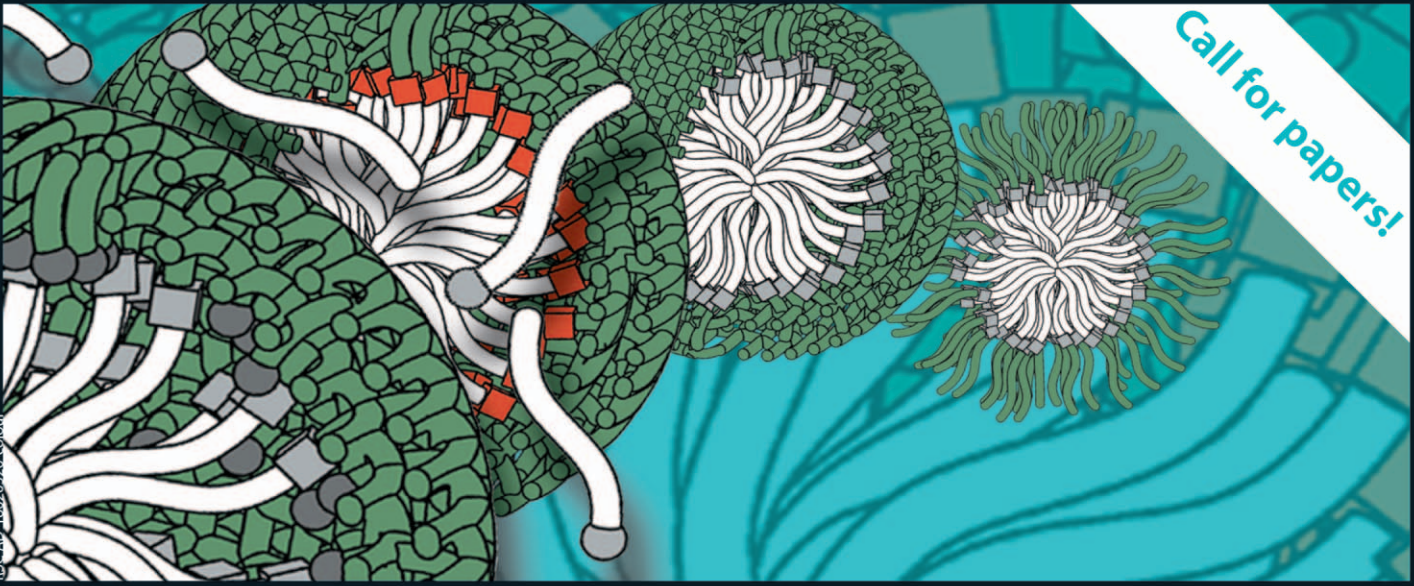
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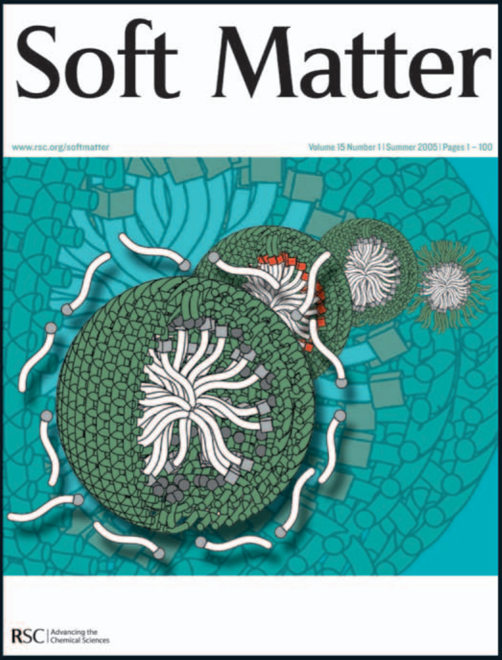
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Highlights

DOI: 10.1039/b502497h

Markus Hölscher reviews some of the recent literature in green chemistry

Tunable desymmetrization of catalytic reactions in supercritical carbon dioxide

Besides the generally acknowledged advantages of supercritical fluids as reaction media, one aspect exists that has not moved entirely into the focus of researchers' attention: the tunability of chemical reactions with respect to various kinds of selectivity. Poliakoff *et al.* from the University of Nottingham have recently contributed a novel example by investigating the etherification of aliphatic diols with different simple alcohols in the presence of an acid catalyst (*J. Am. Chem. Soc.*, 2005, **127**, 293–298). In general, desymmetrization of reactions expands the utility of starting materials without the need to introduce complex protecting group strategies when the desymmetrization enables differentiation between similar functionalities within a molecule. The authors etherificated 1,6-hexanediol with methanol in the presence of an acid catalyst and supercritical CO_2 as reaction medium. In principal the corresponding mono- and bis-ethers should be obtained.

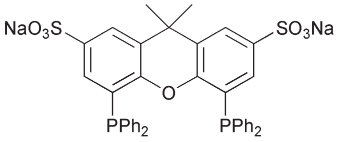
$$HO\text{-}(CH_2)_6\text{-}OH \xrightarrow[scCO_2]{\text{MeOH, cat.}} HO\text{-}(CH_2)_6\text{-}OMe + MeO\text{-}(CH_2)_6\text{-}OMe$$

Interestingly they found the selectivity to depend drastically on the CO_2 pressure applied, with low CO_2 pressures favoring the bis-ether (mono : bis *ca.* 5 : 95) and high CO_2 pressures generating the mono-ether predominantly (mono : bis = 90 : 10). The pressure range in which the selectivity switch occurs is narrow and centred around 90 bar. The authors attribute this unexpected result to the phase behavior of the reaction system. At low pressures the mixture is predominantly biphasic with a considerable amount of liquid phase, whereas at high pressures the mixture occurs mainly as a gas phase. The residence times in the liquid phase and surface tension phenomena related to the wetting of the catalyst bed seem to be the underlying reasons for this elegant desymmetrization reaction.

Highly regioselective hydroformylation SILP catalysts with long term stability

Ionic liquids (ILs) have developed into a true solvent alternative in academia in recent years since they meet the desired chemical and technical requirements to a high extent and are the modern prototypes of green chemicals in many cases. However, from an economic viewpoint conventional solvent systems are still considerably cheaper, which often hinders industrial applications of ILs being put into practice. Furthermore in classic liquid–liquid-multiphase catalysis only a small part of the IL is actively in use during the reaction due to mass transfer limitations of the substrate(s). In a modified approach both problems can be solved at once, by simply introducing an inorganic carrier, which is covered with a thin film consisting of the desired IL and the metal complex used as catalyst. If the thickness of the film is similar to the thickness of the diffusion layer, the metal catalyst (and correspondingly also the IL) could be used completely. Riisager and Wasserscheid *et al.* have exploited this idea for rhodium catalyzed hydroformylation of propene and for the first time developed highly regioselective supported-ionic-liquid-phase (SILP) catalysts with long term stability (*Angew. Chem.*, 2005, **117**, 826–830).

The authors used the sulfoxanthphos ligand **1** to form the catalyst, which was dissolved in IL [bmim][n-$C_8H_{17}OSO_3$]. This solution was applied to partially dehydroxylated silica and, as was shown by comparison with fully hydroxylated silica, dehydroxylation is a prerequisite



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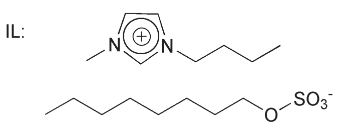
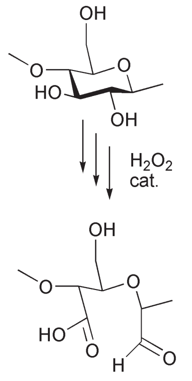


[bmim][n-$C_8H_{17}OSO_3$]

for long term catalyst stability and activity. The derived catalyst maintained its activity and selectivity for at least 60 h on stream in hydroformylation of propene (TOF = 44 h^{-1}, TON *ca.* 2600, *n*/*iso* > 20). Spectroscopic analyses confirmed the reaction to be a truly homogeneous reaction taking place at the metal complex in the IL film. The influence of the carrier was also elucidated: irreversible reactions of ligand and acid silanol groups on the silica surface prior to and during the reaction diminish the amount of ligand available for catalyst formation, which makes clear that a careful treatment of the carrier to reduce the amount of silanol groups is necessary.

Waste-free and clean oxidation of polysaccharides

Non-toxic, biodegradable and abundant natural polymers such as polysaccharides are interesting raw materials, which most of the time have to be modified to meet the demands of many application profiles. Conventional oxidations of polysaccharides are mainly stoichiometric reactions which lead to a large amount of waste (*e.g.* NaOCl method) and consequently the development of clean alternatives constitutes important progress. Sorokin *et al.* from the Institute of Catalysis Research, CNRS, France utilized water soluble tetrasulfonatophthalocyanine metal complexes (MPcS) as catalysts for the oxidation of dry starch in combination with H_2O_2 as oxidant and were able to obtain very encouraging results (*Chem. Commun.*, 2004, 2844–2845). They used different MPcS as catalysts and showed the iron complex to be the most active catalyst with regard to the C2–C3 bond breaking of starch, yielding the corresponding oxidized product with one carboxy and one aldehyde group.

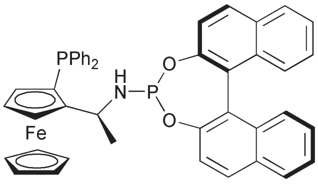


cat. = iron phthalocyanine

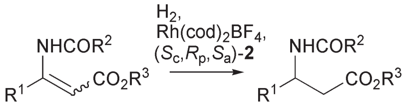
Interestingly the catalyst works best in pure water, and bases and acids lead to poorer catalytic performance. Only small amounts of catalyst are needed to achieve oxidation, and the best results were obtained with a molar substrate : catalyst ratio of 12900 : 1 yielding a TON of 2002, a selectivity on H_2O_2 of 70% and a degree of substitution in carboxyl (DSCOOH) and carbonyl (DSCO) groups of 3.7 and 8.0, respectively. This is a reaction system which meets the conditions of sustainable chemistry, since only a small amount of water and catalyst are needed, H_2O_2 is a green oxidant and the iron phthalocyanine complex is cheap. The product can be recovered without additional treatment almost quantitatively and no waste is generated.

Enantioselective hydrogenation in the presence of ferrocenylphosphine-phosphoramidite ligands

As optically pure β-amino acids are attractive building blocks for biochemical and medicinal applications, straightforward paths for their syntheses are required, one of them being the asymmetric hydrogenation of appropriate prochiral substrates such as β-(acylamino)acrylates. In recent years considerable progress had been made in Rh- and Ru-catalyzed hydrogenations in the presence of different ligands, however many catalytic systems proved successful only in the asymmetric hydrogenation of (*E*)-β-alkyl-β-(acylamino)-acrylates, whereas hydrogenation of the corresponding (*Z*)-isomers was quite unsatisfying. Zheng *et al.* from the Dalian Institute of Chemical Physics showed, very recently, that by combination of ferrocenylphospines and phosphoramidite ligands an active Rh-catalyst can be formed which hydrogenates both the (*E*)- and the (*Z*)-form of β-alkyl-β-(acrylamino)acrylates with high to excellent enantioselectivities up to 98% ee (*Org. Lett.*, 2005, **7**, 419–422).



(S_c,R_p,S_a)-**2**



Furthermore (*Z*)- β-aryl- β-(acylamino)acrylates were also hydrogenated with very high ee's (96–99% ee). The authors noted a peculiarity, upon comparison of the ligand (S_c,R_p,S_a)-**2** used in this study with the otherwise analogous ligand, which bears a methyl substituent at the nitrogen centre. The methyl containing ligand gives far worse enantioselectivities, pointing out the central role of the hydrogen atom present at the nitrogen centre in (S_c,R_p,S_a)-**2**. The authors ascribe this interesting result to a potential second interaction between the N–H proton in the ligand and the substrate.

Towards a mechanism for propene epoxidation over gold–titania catalysts

A synthetic alternative for the production of propene oxide is highly desirable from an environmental standpoint, since the chlorohydrin process has become inappropriate and also in the other known processes considerable amounts of byproducts are generated. It has been known that gold–titania catalysts catalyze the reaction of propene with oxygen in the presence of hydrogen to form propene oxide with a selectivity in the 99% range, which is very advantageous. However, the conversion (below 2%) and hydrogen efficiency (*ca.* 30%) are low. In an analytic approach to unravel the reaction mechanism aiming at rationalized modification of the known gold–titania catalyst, Nijhuis *et al.* from the University of Utrecht analyzed the adsorption properties of pure titania and gold–titania in detail employing IR-spectroscopy (*Angew. Chem.*, 2005, **117**, 1139–1142). To date it has generally been assumed that hydrogen and oxygen form peroxide species on the gold particles and propene is subsequently epoxidized over titanium sites. However, IR analysis leads to a different picture. In an adsorption–desorption experiment it was revealed that propene only desorbs completely when pure titania is used. When gold is present, some of the adsorbed propene remains on the catalyst and forms oxygen bonded bidentate species, as could be shown by comparison with spectra obtained after adsorption of 1,2-propanediol, propene oxide, 2-propanol and 1-propanol. This means, that propene adsorbs onto gold and reacts with surface OH groups. If the system is left in this state carbonate/carboxylate bands form after some time, indicating further reactions and explaining why gold–titania catalysts deactivate over time. When hydrogen and oxygen are added to the catalyst system the bands of the bidentate oxygen bonded species grow significantly faster, and interestingly desorption of this species is also substantially easier. A detailed answer on how exactly the gold particles activate the titania and/or propene has not been given yet, and unambiguous proof that the desorbing species is indeed propene oxide also still needs to be given, but it is clear that the classic mechanism has become obsolete.

£60 million DTI funding for innovative technologies

The British Department of Trade and Industry announced on January 11th the winners of the 2004 competition for funding of innovative technologies with a total grant volume of £60 million. The focus of the supported technology fields clearly lies on environmentally related areas such as technologies to support ‘‘environmentally-friendly transport’’ (£16.6M), ‘‘renewable technologies’’ (£9.3M), ‘‘bio-processing’’ (£6.1M), ‘‘sensor and control systems’’ (£7.2M) and ‘‘advanced composite materials and structures’’ (£5.4M). The DTI’s third call, which will provide £80 million was announced on November 29th, 2004, and funding will be granted to the following areas: design, simulation and modelling, micro and nanotechnology, pervasive computing, waste management and minimisation, smart materials, bio-based industrial products, energy technologies, imaging technologies, opto-electronics and disruptive electronic technologies. Details for this round are available at http://www.dti.gov.uk/technologyprogramme/.

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ZnNaY zeolite catalysed reaction of β-dicarbonyl compounds with ethyl cyanoformate under solventless conditions

Raimondo Maggi,*[ab] Giovanna Bosica,[c] Stefano Gherardi,[ab] Chiara Oro[ab] and Giovanni Sartori[ab]

Received 3rd November 2004, Accepted 28th February 2005
First published as an Advance Article on the web 14th March 2005
DOI: 10.1039/b416665e

A simple and environmentally friendly procedure has been developed for the reaction of β-dicarbonyl compounds with ethyl cyanoformate. The corresponding unsaturated aminoesters were synthesised in good yields (60–95%) and excellent selectivities (96–98%) by carrying out the reaction under solventless conditions in the presence of a Zn-exchanged NaY zeolite. The catalyst can be recovered and reused.

Introduction

In light of stringent and growing environmental regulations, the chemical industry needs to re-examine the most important synthetic processes and to develop more eco-compatible synthetic methodologies.[1] To this purpose heterogeneous catalysis plays a fundamental role, mainly due to its economic and environmental advantages (*i.e.* minimum execution time, low corrosion, waste minimisation, recycling of the catalyst, easy transport and disposal of catalysts).[2]

Another important goal in green chemistry is represented by the elimination of volatile organic solvents; in fact solvent-free organic reactions make syntheses simpler, save energy, and prevent solvent wastes, hazards, and toxicity.[3]

Of course the combination of heterogeneous catalysis with the use of solventless conditions represents a suitable way towards the so-called ideal synthesis.[4] Since the revision of fundamental synthetic reactions under environmentally friendly conditions has been the subject of our research over the last decade,[5] we have recently examined the reaction of β-dicarbonyl compounds with ethyl cyanoformate under zeolite catalysis. This reaction produces unsaturated aminoesters that are useful intermediates for the synthesis of heterocycles,[6] of amino acid derivatives and of other multifunctional derivatives.[7]

Under homogeneous conditions the process is usually carried out in the presence of stoichiometric amounts of Lewis acids[8] or catalytic quantities of zinc or nickel acetylacetonates.[7,9]

Results and discussion

In a first series of experiments we decided to carry out the model reaction between benzoylacetone **1a** (10 mmol) and ethyl cyanoformate **2** (10 mmol) in methylene chloride (5 ml) in the presence of various metal acetates (5% mol) in order to find out the best metal promoter (Scheme 1).

Results concerning the yield and the selectivity of product **3a** are given in Table 1.

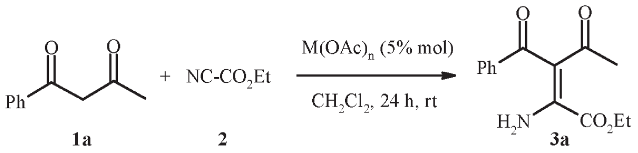
In all cases the reactions are highly selective affording the (*Z*)-isomer; by employing zinc acetate (Table 1, entry c), a good yield was also achieved.

On the basis of these preliminary results, we decided to prepare a Zn-exchanged zeolite to be used as catalyst to perform the reaction under heterogeneous conditions. We singled out zeolite NaY[10] due to its large pores (7.8 Å) that can allow the diffusion of both reactants and products.[11] The zeolite was exchanged with $Zn(NO_3)_2{\cdot}6H_2O$ following the methodology reported in the literature;[12] the final content of Zn in the zeolite was 0.6 mmol g^{-1}.

The model reaction was carried out in the absence of the solvent and was optimised by taking into account the following parameters: reaction time, reaction temperature, and reagents : Zn ions molar ratio. At first, a comparison of the concentration of product **3a** *vs.* time was made (Fig. 1) by carrying out the reaction at 75 °C with 10 mmol of each reagent and 0.50 g of zeolite.

Results show that the maximum production of **3a** occurs during the first 1.5 hours (~60% yield); then the reaction proceeds slowly and the yield reaches its maximum value of 78% after 4 hours.

If the reaction temperature is increased to 100 °C, the product can be isolated in 85% yield.



Scheme 1 Reaction of benzoylacetone with ethyl cyanoformate in the presence of various metal acetates.

Table 1 Reaction of benzoylacetone with ethyl cyanoformate in the presence of various metal acetates[a]

Entry	Catalyst	Yield (%)	Selectivity (%)
a	$Ni(OAc)_2{\cdot}4H_2O$	54	98
b	$Mn(OAc)_3{\cdot}2H_2O$	5	97
c	$Zn(OAc)_2$	61	97
d	$Co(OAc)_2{\cdot}4H_2O$	46	96

[a] Reaction conditions according to ref. 9.

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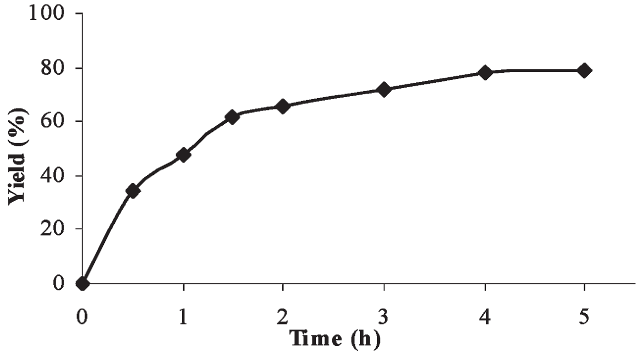


Fig. 1 Reactivity of benzoylacetone with ethyl cyanoformate in the presence of ZnNaY zeolite at 75 °C as a function of time.

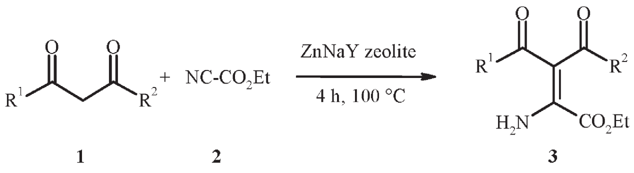
The effect of the catalyst amount was then investigated. To this end the same model reaction was carried out in the presence of 0.10 g, 0.25 g, 0.50 g and 1.00 g of ZnNaY zeolite at 100 °C for 4 hours; product **3a** was obtained in 26%, 59%, 84% and 85% yields respectively. These data show that the optimum catalyst : reagents ratio was 0.25 g : 10 mmol.

To explore the general validity of this process, different β-dicarbonyl compounds, namely β-diketones, β-ketoesters and β-diesters were reacted with ethyl cyanoformate by stirring the mixture at 100 °C for 4 hours in the presence of ZnNaY zeolite; results are given in Table 2.

The reaction is of general applicability and affords good yields with β-diketones and β-ketoesters. On the contrary, due to the lower reactivity of β-diesters, the corresponding products were isolated in poor yield; moreover, in all cases excellent selectivity was observed (>96%).

Finally we faced the problem of catalyst leaching and recycling. The actual heterogeneity of the process was examined by following the standard procedure suggested by Lempers and Sheldon.[13] Thus the reaction mixture was filtered at 100 °C after 1 hour (when product **3a** had been produced in 50% yield) and the filtrate was heated at 100 °C for a further 3 hours. Product **3a** was detected in 52% total yield (50% + 2%). In contrast, addition of both reagents (10 mmol each) to the recovered solid catalyst and heating at 100 °C for 4 hours afforded the unsaturated aminoester **3a** in 85% yield. These results confirm that the reaction really occurs on the supported metal sites.

Table 2 Synthesis of variously substituted unsaturated aminoesters **3**



Entry	R^1	R^2	**3** Yield [sel.] (%)
a	Ph	Me	**3a** 84 [97]
b	Me	Me	**3b** 99 [99][a]
c	Me	OEt	**3c** 70 [98]
d	OEt	Ph	**3d** 65 [96]
e	Me	OMe	**3e** 72 [97]
f	OMe	OMe	**3f** 10 [98]
g	OEt	OEt	**3g** 12 [98]

[a] Reaction carried out at rt.

In addition, after filtration, washing with methanol and acetone, and drying, the ZnNaY zeolite was reused for three times affording the product with the same high yield (reaction: 87%; 1st recycle: 85%; 2nd recycle: 84%; 3rd recycle: 85%).

Conclusions

In conclusion, we have reported a new, effective and environmentally friendly methodology for the preparation of variously substituted unsaturated aminoesters starting from β-diketones or β-ketoesters and ethyl cyanoformate. These compounds can be synthesised in high yield and with excellent selectivity by using a zinc-exchanged NaY zeolite and avoiding the use of any solvent. In addition the catalyst can be recovered by filtration and utilised at least four times without lowering its activity.

Experimental

Typical procedure

A mixture of the selected β-dicarbonyl compound (10 mmol), ethyl cyanoformate (10 mmol) and ZnNaY zeolite (0.25 g) was heated in an oil bath at 100 °C for 4 hours, with magnetic stirring. The flask was equipped with an air condenser and left open throughout the course of the reaction. After cooling to rt, the catalyst was removed by filtration and washed with methanol (20 ml) and acetone (10 ml); the solvents were distilled off and the crude product was purified by crystallisation from ethyl acetate. Satisfactory IR, MS, ^{1}H NMR, and mp data were obtained for all the unsaturated aminoesters **3**, results were consistent with those found in the literature.[7,14]

Acknowledgements

We thank the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR), Italy, and the University of Parma (National Project "Processi puliti per la Chimica Fine") for their support. We are also grateful to the Centro Interfacoltà Misure (CIM) for the use of NMR and mass spectrometry instruments. Prof. Claudio Mucchino is thanked for ICP analysis.

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Toxicity and antimicrobial activity of imidazolium and pyridinium ionic liquids

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Received 23rd December 2004, Accepted 28th February 2005
First published as an Advance Article on the web 14th March 2005
DOI: 10.1039/b419172b

Ionic liquids (ILs) are novel organic salts with a wide liquid range that have enormous potential for industrial use as "green" chemicals. Varying the cationic and anionic components can alter IL properties and toxicities. Before the likely industrial release of ILs into the environment, it is necessary to determine their toxic and antimicrobial properties. As a measure of microbial toxicity of imidazolium and pyridinium ILs with varying alkyl chain lengths, we investigated *Vibrio fischeri* using the Microtox method. An increase in alkyl group chain length as well as an increase in the number of alkyl groups substituted on the cation ring corresponded with an increase in toxicity. Varying the anion identity did not significantly alter toxicity. We then examined the antimicrobial effects of 1000 ppm of butyl-, hexyl- and octyl- imidazolium and pyridinium bromide ILs on the growth of a group of microorganisms representing a variety of physiological and respiratory capabilities. In general, hexyl- and octyl- imidazolium and pyridinium bromides had significant antimicrobial activity to pure cultures of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas fluorescens* and *Saccharomyces cerevisiae*. Butyl-imidazolium and pyridinium bromides were less antimicrobial than ILs with longer alkyl chain lengths to all microorganisms examined. However, the most significant antimicrobial activity was observed in tests with *B. subtilis*. This research provides toxicity and antimicrobial information about ILs, prior to their widespread use and release. This type of proactive approach can aid in the prevention of pollution, and avoid costs of future clean-up, and provide information about the "green" nature of practical industrial solvents.

Introduction

In the past several years, there has been a dramatic increase in the synthesis of novel "green" imidazolium and pyridinium ionic liquids (ILs). Chemical engineers have been developing ILs to replace conventional volatile organic solvents that contribute to serious air pollution.[1] Ionic liquids are one class of chemicals that have potential as benign industrial alternatives; these organic salts have vanishingly low vapor pressures, and are liquid at ambient conditions, and do not evaporate or cause air pollution.[2] Substitution of ILs for traditional solvents could potentially improve environmental health while saving industry billions of dollars in future environmental mitigation and clean-up.[1]

Ionic liquids are designed with large organic cations, such as imidazolium or pyridinium, with alkyl chain substituents that alter the hydrophobicity of the molecule (Fig. 1). Common IL anions include hexafluorophosphate (PF_6^-), tetrafluoroborate (BF_4^-), chloride (Cl^-), nitrate (NO_3^-) and bromide (Br^-). Ionic liquids vary in stability to moisture and solubility in water, polar and nonpolar organic liquids. Designer engineering has made ILs suitable for many applications, including electrolytes in batteries, metal catalysts, solvents in liquid–liquid extractions, and many reactions, including hydrogenations, Diels–Alder reactions, alkylations and others.[1,3–6]

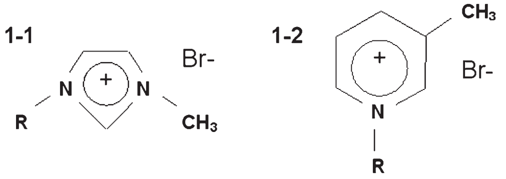

Fig. 1 Chemical structure of 1-alkyl-3-methyl imidazolium (1-1) and 1-alkyl-3-methyl pyridinium (1-2) bromide.

However, while ILs may reduce the costs and environmental mitigation of air pollution, release of ILs into aquatic environments may lead to water pollution, because of their high solubilities. Gorman-Lewis and Fein have shown that the IL 1-butyl-3-methyl imidazolium chloride (bmimCl), would be minimally retained by geologic adsorption in non-interlayer clay systems.[7] This would result in unimpeded transport of the chemical through subsurface groundwater. For this reason, it is critical to determine the toxicities of ILs prior to their release into the environment. The boom of designer solvent synthesis has sparked a corresponding increase in rapid IL toxicity testing, to determine the effective concentration at 50% (EC-50 value). EC-50 values can then be related to the activity of the compound of interest using quantitative structure–activity relationship (QSAR) models. By determining IL toxicity to test organisms, engineers can tailor IL-synthesis to particular industrial processes, while preventing the use of compounds that are harmful to the environment.

Bacteria have short generation times and serve as ideal starting points for IL structure–activity relationship investigations.

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Early examinations have shown quaternary ammonium (QA) and pyridinium compounds to have significant toxic effects on a variety of bacteria and fungi.[8–10] The antibacterial potential of imidazolium, pyridinium and QA ILs has been the source of several recent publications. Pernak *et al.* observed a trend of increasing toxicity with an increase in the C-1 alkyl chain length substituent in pyridinium, imidazolium, and QA salts to various bacteria.[11–14] This trend was also observed by Ranke *et al.* in ILs containing C_3mim to C_{10}mim cations and BF_4^-, PF_6^- and Cl^- anions to *Vibrio fischeri*, IPC-81 cells and C_6 glioma cells.[15] Additionally this trend has been shown to extend to higher organisms, including *Caenorhabditis elegans* and *Daphnia magna*.[16,17] Varying the anion has minimal effects on toxicity of several pyridinium and imidazolium compounds, indicating that IL toxicity is largely driven by the alkyl chain branching and hydrophobicity of the cation.[11,15,17] Pyridinium, imidazolium and pyrrolidinium ILs have recently been nominated to the United States National Toxicology Program (NTP) for toxicological testing, based upon their widespread interest as possible alternatives to organic solvents.[18]

We present an examination of the toxicity of a variety imidazolium and pyridinium-cation ILs to a range of micro-organisms. Specifically, we focused on the toxicity and antimicrobial activity of 6 compounds with increasing length alkyl chain substituents: 1-butyl-3-methyl imidazolium bromide (bmimBr), 1-hexyl-3-methyl imidazolium bromide (hmimBr), 1-octyl-3-methyl imidazolium bromide (omimBr), 1-butyl-3-methyl pyridinium bromide (bmpyrBr), 1-hexyl-3-methyl pyridinium bromide (hmpyrBr) and 1-octyl-3-methyl pyridinium bromide (ompyrBr). The combination of toxicity and antimicrobial activity tests provides a study of the effects of the imidazolium and pyridinium bromide IL series to a diverse group of microorganisms. It serves as a basis for further toxicity tests to higher organisms and more complex systems, as well as a guide for further synthesis of environmentally benign compounds.

Results and discussion

The trend of increasing toxicity to *V. fischeri*, with increasing hydrophobicity, corresponding to an increasing alkyl chain length of the C-1 substituted groups was observed in the 1-alkyl-3-methyl imidazolium and 1-alkyl-3-methyl pyridinium bromide series ($p < 0.05$, $n = 9$, at all time points, Fig. 2, Table 1). Thus, those ILs with longer alkyl chains on the cations were more toxic. In comparison to some commonly used industrial solvents, the octyl- and hexyl-substituted ILs examined are more toxic. Toxicity in the butyl-substituted compounds, however, falls among some of the less toxic conventional volatile organic solvents (Table 1). Butyl-substituted ILs also have much lower octanol–water partition coefficient values (log P), and are more water soluble (Table 1).

We also observed a trend of increasing toxicity to *V. fischeri* with increased substitution of methyl groups around the pyridinium ring in both the bromide (Br^-) and dicyanamide ($N(CN_2)_2^-$) anion series. Cation toxicity increases from 1-butyl pyridinium to 1-butyl-3-methyl pyridinium and then to 1-butyl-3,5-dimethyl pyridinium ($0.002 < p_{DCA} < 0.079$; $0.000 < p_{Br} < 0.909$; $n = 6$, at 15 minutes). This trend also corresponds to increasing hydrophobicity of the molecule.

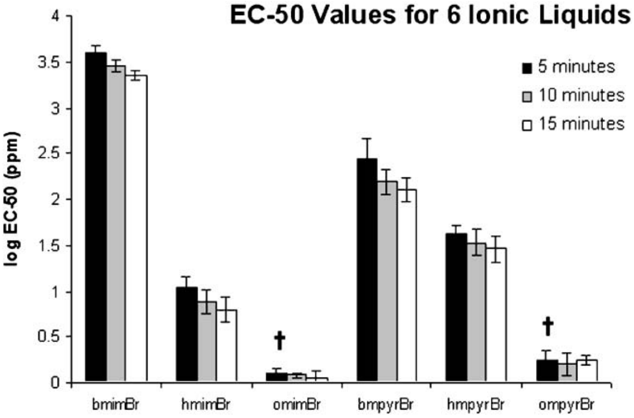

Fig. 2 Acute toxicity values for 3 imidazolium and 3 pyridinium bromide ionic liquids at 5, 10 and 15 minutes, expressed as average log EC-50 in ppm ($n = 3$) ± standard deviation. † indicates no significant difference between omimBr and ompyrBr EC-50 values.

Imidazolium and pyridinium toxicities were not directly comparable. bmimBr was significantly less toxic than bmpyrBr ($p = 0.001$, $n = 6$ at 5 minutes), but hmimBr was more toxic than hmpyrBr ($p = 0.003$, $n = 6$ at 5 minutes); and omimBr and ompyrBr have similar toxicities ($p = 0.106$, $n = 6$ at 5 minutes). While a trend of increasing toxicity with increasing exposure time from 5 to 10 to 15 minutes is observed (Fig. 2), this trend was not significant in any chemical examined. This suggests that the majority of the toxic effect of ILs is acute to *V. fischeri*, inhibiting organism respiration.

To further determine the inhibitory effects of ionic liquids, we examined the antimicrobial activity of 6 ILs to a diverse set of microorganisms, representing Gram positive and negative rods, a Gram positive coccus and a yeast. Similar trends of increasing antimicrobial activity corresponding to increased alkyl chain length of the C-1 substituent group were observed in these tests (Fig. 3). For all 5 microorganisms examined, omimBr and ompyrBr inhibited colony formation the most effectively. The hexyl-group ILs exhibited less pronounced inhibitory effects, and butyl-groups ILs were only slightly different than the buffer control. While butyl-substituted ILs did not display dramatic acute antimicrobial effects, they do have significant acute and chronic effects to higher organisms, particularly *Daphnia magna*.[17] It has also been suggested that 1-butyl-3-methyl imidazolium chloride (bmimCl) and 1-butyl pyridinium chloride (bpyrCl) may have similar activity to the carcinogenic pesticide paraquot (1,1′-dimethyl-4,4′-bipyridinium chloride), which produces superoxide radicals that attack lipids in cytoplasmic membranes.[18] Further studies investigating the chronic toxicities of these low-acute toxicity ILs are necessary, particularly if environmental groundwater release will only be minimally impeded and contaminant transport levels are high.[7] The antimicrobial effects of the octyl-substituted compounds depended upon the microorganism examined. All ILs were most inhibitory to *B. subtilis* (aerobe), a Gram positive rod. *S. aureus* (facultative anaerobe), a Gram

Table 1 Molecular weight (M), octanol–water partition coefficients (log P) and toxicity expressed as EC-50 ± standard deviation (ppm) and log EC-50 for several ionic liquids and other common volatile organic compounds. EC-50 values are averages (n = 3) from 15 min. Microtox Acute Toxicity tests; results are grouped by log EC-50 values from highest to lowest toxicity. Common VOC EC-50 values are indicated in bold; ILs used in further antimicrobial tests are italicized. Log P values were obtained from Lide *et al.*[19] for VOCs and from Ropel *et al.*[20] for ILs. EC-50 values for VOCs are for 30 minute acute toxicity tests to *Photobacterium phosphoreum*[21]

Chemical name	MW	(log P)	EC-50	EC-50 error	log EC-50
1-Octyl-3-methyl imidazolium bromide	*275.19*	*∼0.8*	*1.17*	*0.19*	*0.07*
1-Octyl-3-methyl pyridinium bromide	*286.19*	*∼0.8*	*1.77*	*0.20*	*0.25*
1-Hexyl-3-methyl imidazolium bromide	*247.14*	*∼0.15*	*6.44*	*1.82*	*0.81*
***o*-Xylene**	**106.18**	**3.12**	**9.25**	—	**0.97**
1-Hexyl-3-methyl pyridinium bromide	*258.14*	*∼0.15*	*29.99*	*10.83*	*1.48*
Phenol	**94.12**	**1.48**	**30.76**	**7.21**	**1.49**
Toluene	**92.15**	**2.73**	**31.74**	**15.82**	**1.50**
1-Butyl-3,5-dimethyl pyridinium N(CN$_2$)$_2$	231.25	—	55.71	23.27	1.75
Methyl isobutyl ketone	**100.16**	**1.31**	**79.60**	**0.00**	**1.90**
1-Butyl-3-methyl pyridinium N(CN$_2$)$_2$	216.22	∼ −2.4	98.00	10.20	1.99
Benzene	**78.12**	**2.13**	**108.05**	**85.77**	**2.03**
3-Methyl pyridine (starting compound)	94.08	—	110.60	19.60	2.04
1-Butyl-3,5-dimethyl pyridinium bromide	244.11	—	119.27	23.88	2.08
1-Butyl-3-methyl pyridinium bromide	*230.09*	*∼ −2.4*	*130.48*	*39.41*	*2.12*
1-Butyl pyridinium N(CN$_2$)$_2$	203.21	—	409.92	97.68	2.61
1-Butyl pyridinium chloride	172.62	—	439.97	84.27	2.64
1-Butyl pyridinium bromide	217.07	—	538.40	14.58	2.73
Ethylene glycol	**62.07**	**1.2**	**621.00**	—	**2.79**
1-Butyl-3-methyl imidazolium chloride	174.63	−2.4	897.47	283.58	2.95
1-Butyl-3-methyl imidazolium N(CN$_2$)$_2$	205.22	∼ −2.4	966.24	229.39	2.99
Chloroform	**119.38**	**1.97**	**1199.33**	**1127.51**	**3.08**
3-Methyl imidazole (starting compound)	83.07	—	1218.20	86.40	3.09
1-Butyl-3-methyl imidazolium bromide	*219.08*	*−2.48*	*2248.38*	*274.01*	*3.35*
Dichloromethane	**84.93**	**1.25**	**2532.33**	**1415.38**	**3.40**
Ethyl acetate	**88.12**	**0.73**	**5822.00**	—	**3.77**
Acetone	**58.08**	**−0.24**	**19311.14**	**5295.78**	**4.29**
Methanol	**32.04**	**−0.74**	**101068.50**	**113703.83**	**5.00**

positive cocci, and *S. cerevisiae*, a yeast, were least affected by the IL treatments. However, *E. coli* (facultative anaerobe) and *P. fluorescens* (aerobe), both Gram negative rods, were significantly affected by the IL-treatments. The observation that all ILs showed the greatest inhibition to *B. subtilis* does not appear to be related to the cell wall characteristics of the microorganism. *S. aureus* also has a Gram positive cell wall, but did not exhibit the highly significant antimicrobial IL effects seen for *B. subtilis*. Thus, inhibitory effects for *B. subtilis* may be related to some other physiological characteristics not determined by this study.

Since the trend of increased growth inhibition with longer alkyl chain length holds for all microorganisms examined, the toxic effect may be related to a common cellular structure or process. Others have suggested that the mechanism of toxicity for ILs is through membrane disruption because of the ILs structural similarity to detergents, pesticides and antibiotics that attack lipid structure.[8,12,13,18] Many ILs are similar to cationic surfactants that induce polar narcosis due to their interfacial properties, and may cause membrane-bound protein disruption.[22] Another suggested mechanism of IL toxicity is related to acetylcholinesterase inhibition in more complex test organisms, such as the electric organ in *Electrophorus electricus*.[23,24] In future studies, we will use bacterial model systems to further examine the mechanism of IL toxicity, focus on the mutagenicity of ILs, and determine if this mechanism is common to more complex test organisms.

Ionic liquids are currently being designed and studied for practical and environmentally-friendly industrial application. The low volatility usually associated with ILs, compared to traditional industrial solvents would result in lower emissions and improved air quality. However, our study indicates that some ILs are even more toxic to microorganisms than traditional solvents (Table 1). Our results suggest that antimicrobial effects should be considered in the overall evaluation and design of ionic liquids.

Experimental

Acute toxicity tests

Ionic liquids were prepared by Dr. Mark Muldoon, Department of Chemical Engineering, University of Notre Dame, using standard procedures.[25–27] The ILs were then diluted to 10 000 ppm in sterile distilled water. Three replicated EC-50 (effective concentration at 50%) values at 5, 10 and 15 minutes were determined for each IL. EC-50s were determined using the Microtox M500 Rapid Toxicity Testing System (Azur Environmental, Strategic Diagnostics, Newark, DE) and the ASTM standard toxicity protocol.[28] The Microtox method uses the amount of light output from a culture of *Vibrio fischeri* NRRL B-11177. Bacterial bioluminescence is directly linked to cellular respiration, so a decrease in luminescence corresponds to cellular toxicity.

Antimicrobial activity

Cultures of *E. coli*, *S. aureus* and *B. subtilis* were grown on Trypticase Soy (TS) plates (Fisher Scientific) for 24 h at 37 °C.

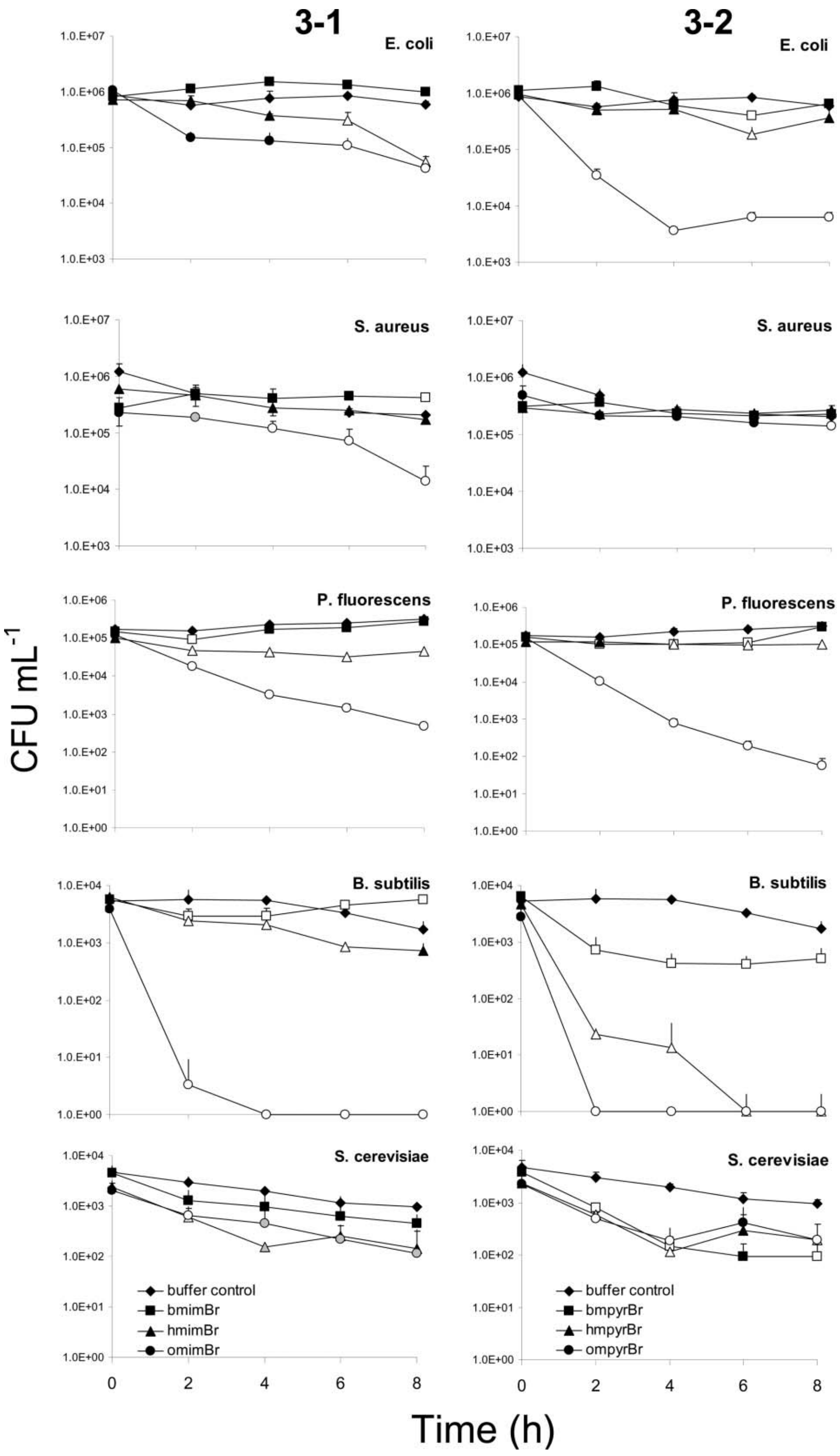

Fig. 3 Inhibitory effects of imidazolium (3-1) and pyridinium (3-2) ionic liquids to 5 microorganisms over an 8 h exposure time. Each data point represents an average of colony forming units (CFU) mL^{-1} ± standard deviation (n = 3). Symbols in black are not significantly different from the buffer control; symbols in white are significantly different from the buffer control; symbols in gray are marginally different from the control. Significance is assessed at $p = 0.05$, using Repeated Measures ANOVA through time, followed by One-Way ANOVAs and Fisherã s LSD pairwise comparisons at each time point.

P. fluorescens was grown on TS agar for 48 h at 25 °C and *S. cerevisiae* was grown for 48 h on Yeast Maintenance (YM) agar (Difco) at 30 °C. Single colonies of each organism were removed and recultured in 25 mL of TS or Yeast Extract Peptone Dextrose (YEPD) broth (Difco) under the same growth conditions.

Pure cultures in broth were then diluted to an optical density of 0.1 at 550 nm in sterile 0.85% NaCl buffer solution to standardize total colony numbers being tested for antimicrobial activity of ILs. 0.5 mL of diluted cell culture was then inoculated into 3 replicates of 5 mL of 0.22 μm filter-sterilized 0.85% NaCl (positive control), and 1000 ppm each of bmimBr, hmimBr, omimBr, bmpyrBr, hmpyrBr, ompyrBr and bleach (negative control). Immediately after inoculation, each replicate of culture-in-IL treatment was serially diluted to 10^{-1}, 10^{-2}, 10^{-3}, and 10^{-4} in 4.5 mL of sterile 0.85% NaCl buffer solution. Then 100 μL of each dilution was plated on TS agar or YM agar. Plate cultures were allowed to grow for their respective optimal growth conditions and viable colony numbers were determined.

Statistical methods and analysis

EC-50 values were calculated according to the Microtox Acute Toxicity Test (Azur Environmental, Strategic Diagnostics, Inc.). Repeated Measures ANOVAs, One-Way ANOVAs and Fisher's LSD Pairwise Comparisons were conducted using Systat Version 10 (SPSS, Inc. 2000).

Acknowledgements

Graduate Assistance in Areas of National Need (GAANN) Fellowship Program, National Science Foundation Graduate Research Fellowship Program, National Oceanographic and Atmospheric Administration, Indiana 21st Century Research and Technology Fund, Dr. Joan Brennecke, Dr. Mark Muldoon, Laurie Ropel, Jacob Crosthwaite, Meghan Perks, Dr. Randall Bernot.

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Properties and potential applications of natural cellulose fibers from cornhusks

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Received 29th September 2004, Accepted 10th January 2005
First published as an Advance Article on the web 1st February 2005
DOI: 10.1039/b415102j

For the first time, natural cellulose fibers having properties between cotton and linen and suitable for various industrial applications have been extracted from cornhusks. High quality cellulosic fibers from cornhusks mean food, clothing and other major industrial products from the same source without the need for any additional natural resources. Using cornhusks for fibrous applications would save the land and other natural resources required to grow fiber crops and will conserve the non-renewable petroleum sources required to produce synthetic fibers. More than 9 million tons of natural cellulose fibers with a potential sale value of $19 billion with a value addition of at least $12 billion can be produced from the cornhusks available every year. Utilizing cornhusks as a source for natural cellulose fibers will significantly benefit the agriculture, fiber, food and energy needs of the future and will also benefit the environment.

Introduction

For years, textile and other industries using fibers have been attempting to find new sources of natural fiber that could; compare with the performance properties of major natural fibers like cotton and linen; reduce the dependence on land and other resources required to produce fibers, and compete in terms of cost and availability with currently available fibers. We believe we have finally found such a fiber source in cornhusks. Current applications of cornhusks hydrolyze the cellulose into single fibers or individual cells of about 0.5 to 1.5 mm in length, too short to be used for textile and other industrial applications.[1] For the first time, we have obtained natural cellulosic fibers from cornhusk with structure and performance properties that would make it appropriate for various high quality fibrous applications. Fibers here refer to a bundle of individual cells held together by hemicellulose, lignin and other non-cellulosic substances.

Attempts to use the by-product of a major food crop as a source for fibers will be significant since the world's growing population will require more efficient land use in order to feed and clothe those in the poorer parts of the world.[2–5] Cornhusks offer an annually renewable, low cost, and copious source for cellulosic fibers. In addition, the process of fiber extraction from cornhusks requires relatively lesser energy and is also environmentally friendly.

The main environmental benefit of using corn fiber is, as stated above, the conservation of land and resources by creating fiber and food from the same plant. Attempts have been made to use the by-product of other food sources like pineapple and banana leaves, sugarcane rind and coconut husks as sources for natural cellulose fibers.[6–9] However, fibers obtained from these by-products have limitations in quality, availability and geographical requirements necessary to grow these crops.[10–12] By comparison, cornhusk is commonly available, with no geographical limitations, and is of limited commercial value at present. Therefore, cornhusks show greater promise in providing large quantities of natural cellulose fibers with significant economic benefits than any other agricultural by-product.

The economic feasibility of developing cornhusk as an alternative to natural fibers also looks promising, especially when compared to the potential availability and production cost of other natural fibers. In 2002, world cotton production was about 20 million tons and the average selling price was $1.30 per kilogram.[13] All other natural cellulosic fibers such as ramie, linen, jute, sisal and coir accounted for about 5.0 million tons.[13] Annual world corn production is about 640 million tons which generates about 45 million tons of cornhusk.[14] Based on the fiber production method reported in this paper, the available cornhusks can be used to produce at least 9 million tons of fiber every year with a production cost competitive to cotton.

The production costs of cornhusk fiber are currently estimated at $0.50 to $0.80 per kilogram depending on the country of production. The labor component is about 60% of the cost, making it one of the cheapest available natural fibers, even in comparison to cotton which has production costs ranging from $0.50 to $2.50 per kilogram.[15] With the potential availability of about 9 million tons of corn fiber, a sale value of more than $19 billion with a value addition of about $12 billion is possible every year (assuming a competitive selling price of $2.20 per kilogram of cornhusk fiber).

However, these benefits cannot be realized unless cornhusk fibers are suitable for industrial applications, especially for textile goods which demand fibers of high quality. To evaluate the suitability of cornhusk fiber for industrial applications, we will compare the properties of cornhusk fiber with cotton, linen and jute, the three most common natural fibers. In this paper, we will demonstrate the suitability of cornhusk fibers for high value applications by examining the structure and properties of the fibers extracted from cornhusks. The

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introduction of corn fibers will create a new class of natural fiber, the "husk fiber", to existing seed, bast and leaf classes.

Experimental

Materials

Cornhusks were collected from fully mature corn plants in the greenhouses at the University of Nebraska, Lincoln and from the corn fields in Nebraska. These cornhusks were cleaned by hand to remove the tassel, leaves and other parts of the corn plant. The cornhusks were cut into lengths of about 2 to 3 cm using an Ingento model A6T paper cutter mounted on a table. The cornhusks were cut in order to obtain fibers that had lengths similar to cotton and suitable for processing on the cotton spinning system.

Fiber extraction

Fibers were obtained from cornhusks by a combined chemical and enzymatic extraction. Cornhusks were treated with 0.5 N sodium hydroxide solution for 60 minutes at 95 °C with 5% of cornhusks by weight in the alkali solution. The treated slurry was washed in water to remove the dissolved substances and the coarse fibers obtained were neutralized using 10% (v/v) acetic acid solution. The neutralized fibers were dried under ambient conditions. Two types of enzymes, pulpzyme and cellulase supplied by Novozymes, Franklinton, NC, were used to remove the lignin and hemicellulose from the cornhusks.

Pulpzyme is a xylanase that depolymerizes hemicellulose and breaks the covalent link between lignin and carbohydrates in the cornhusks. The depolymerized hemicellulose and separated lignin are removed during washing. Cellulases are enzyme complexes that are composed of the three main units endoglucanases, cellobiohydrolases and β-glucosidases. The endoglucanases attack the cellulose chains at random, cellobiohydrolases hydrolyze the cellulose chains from the non reducing end and β-glucosidases hydrolyze the cellulobiose into glucose.[16] Cellulase was used in this study to remove the short fibers in the cornhusks. The short fibers are unsuitable for textile applications and relatively easy to hydrolyze. However, as with the alkali pretreatment, choosing the concentration, time and temperature of enzyme treatment is critical since cellulases are capable of damaging the cellulose in cornhusks resulting in decreased fiber strength.

An enzyme concentration of 5% on the weight of the fibers with about 5% (w/v) of fibers in the enzyme solution, treatment time of 60 minutes at 50 °C was found to produce fibers with the desired quality. Fibers obtained after the enzyme treatment were washed in water and dried under ambient conditions.

Fiber bleaching

Corn fibers obtained from the combined chemical and enzymatic extraction were bleached using 3 g l^{-1} of 30% hydrogen peroxide at 90 °C for 60 minutes with about 7% (w/v) of fibers in the bleaching solution. 10 g l^{-1} of sodium silicate was used as a stabilizing agent along with 0.5 g l^{-1} of sodium hydroxide and 1.8 g l^{-1} of sodium carbonate to maintain the pH at 10.5. After bleaching, the fibers were washed and dried at ambient conditions. The bleached fibers were tested to evaluate the effects of bleaching on the color, fineness and strength of the fibers.

A Hunterlab UltrascanXE spectrophotometer was used to determine the color of the unbleached and bleached fibers. The color of the fibers was measured in terms of the Yellowness Index (YI) and Whiteness Index (WI) according to ASTM standard E313-98.[17]

Fiber characterization

The amount of pure cellulose in the corn fibers was determined using the Norman and Jenkins method.[18] Fiber fineness (linear density) was calculated in terms of denier, defined as the weight in grams per 9000 m of the fiber, by weighing a known length of the fibers. Tensile properties of the fibers were obtained using an Instron fiber testing machine. A gauge length of 25 mm and crosshead speed of 18 mm min^{-1} was used. Five sets of twenty fibers each were tested to determine the denier and tensile properties. The average strength, elongation, modulus and work or rupture are reported along with the standard deviation between the sets of fibers tested. Moisture regain of the fibers was determined using ASTM method D 2654. Standard test conditions of 65% relative humidity and temperature of 21 °C were used for all the tests.

Morphological structure

A Hitachi model S2000N SEM was used to investigate the morphological characteristics of individual fibers and fiber bundles. For observation in the SEM, the fibers were laid down on an aluminium stub using a conductive adhesive tape and were sputter-coated with gold palladium prior to observations. Cross-sections of the samples were prepared according to standard methods.[19] An Olympus AX70 fluorescence microscope with 40 × lens was used to observe the cross-sections of untreated cornhusks and the extracted fibers.

Physical structure

X-Ray diffraction was used to study the physical structure of the fiber along with its constituents. X-Ray diffraction patterns of corn fibers were recorded from $2\theta = 0°$ to $30°$ using a Philips PW 1050/81 diffractometer. Specimens to be observed were powdered in a Wiley mill to pass a 2 mm mesh. The powder was mounted into a cavity holder to record the X-ray diffraction. The degree of crystallinity was calculated by integrating the area under the diffracted peaks after accounting for the amorphous and background scatter. Crystallite size was calculated using the Scherer's equation.[20] X-Ray diffraction pictures were obtained using a Bruker smart apex ccd camera. Averages of 8 readings were taken, each for 300 seconds at a sample to detector distance of 5.9 cm.

Results and discussion

Fiber extraction

Natural cellulosic fibers (excepting cotton and kapok) are multicellular and are used in industrial applications as groups of individual cells, known as fiber bundles.[7] In cornhusk, individual cells as reported in Table 1 are too small to be used

Table 1 Comparison of cornhusk fiber composition with cotton, linen and jute

Fiber/bundle	Cellulose (%)	Color	Fiber length/cm	Unit cell dimensions Length/mm	Unit cell dimensions Width/μm
Corn	**80–87**	**Yellowish white**	**2–20**	**0.5–1.5**	**10.0–20.0**
Cotton	88–95	Off white	1.5–5.5	15.0–56.0	12.0–25.0
Linen	72–82	Creamy white	20–140	4.0–77.0	5.0–76.0
Jute	62–64	Brownish	150–360	0.8–6.0	15.0–25.0

Data for cotton, linen and jute fibers are from refs 7, 21 and 22.

for textile and other industrial applications. Lignin, hemicellulose and other binding substances, bind individual cells into a fiber bundle suitable for textile and other industrial applications.[7] Fiber bundles are obtained from larger vascular bundles in plants by partially removing lignin and other constituents such as hemicellulose, pectin and wax in a process called retting, that may employ bacteria and fungi in the atmosphere, chemicals, and enzymes.[10,11] However, an alkaline pretreatment and enzyme extraction is needed to obtain high quality fiber from cornhusks.

Using only the alkali to extract fibers from cornhusks resulted in either coarse, low quality fiber or in small hydrolyzed fibers. The coarser fibers obtained at low concentration of alkali, shorter time and lower temperature had deniers of about 180 and higher. The strength of these fibers was low at about 1 gram per denier. Some of the possible reasons for the lower strength of the coarser fibers are discussed later in the text. At higher concentration of alkali, higher treatment time or temperature, most of the cellulose in the cornhusks was hydrolyzed into small fibers and the fiber yield was also low. Hydrolysis of cornhusks results in individual cells which are only about 0.5 to 1.5 mm in length as reported in Table 1.

Enzymes by themselves are unable to break the outside layer of protective material on the cornhusks. Varying the concentration of enzymes, pH, time and temperature of treatment resulted in the removal of the weak fibrous parts that connect the long thick strands in cornhusks. The thick strands of cornhusk retained the outer covering even after the enzyme treatment. Therefore, a mild alkaline treatment is required to remove the surface substances and allow the enzymes to be functional for the removal of part of the lignin and cellulose.

However, as mentioned earlier, the quality and yield of fibers are dependent on the treatment conditions such as alkali and enzyme concentration, time and temperature. Typical fiber yields after the alkali pretreatment and enzyme extraction ranged from 15–20% with fiber fineness between 12–120 denier. The combination of chemical pretreatment and enzyme extraction under conditions specified above results in partial delignification and produces high quality fibers with the required fineness, length, strength, and elongation without hydrolyzing the cornhusk into individual cells.

Fiber composition and structure

The chemical composition and physical and morphological structure of fibers are the descriptive properties that determine a fiber's properties, like strength, elasticity, and water absorbance. Examining the chemical composition and structure of the fibers in comparison to other natural cellulosic fibers can be useful in evaluating the utility of the corn fibers.

Chemical composition

Natural cellulosic fibers contain anywhere between 60–95% cellulose. Hemicellulose, lignin, pectin, waxes, and proteins are the remaining constituents, their proportion depending on the conditions of growth, fiber source, and method of fiber extraction. Table 1 shows that corn fibers contain about 80–87% cellulose, a relatively higher quantity when compared to linen and jute. Most of the hemicellulose is removed during fiber extraction and the remaining hemicellulose, lignin and pectin hold the individual cells in the form of a fiber bundle.

While the non-cellulosic constituents are desirable in their cohesive properties, their presence imparts a natural color to the fiber, which could be removed by bleaching, a process required for producing white fibers or their products. The coarse fibers produced after the alkaline pretreatment are yellow in color mainly due to the presence of lignin in the fiber.

Physical structure

The physical structure of a fiber describes the amount of crystalline (ordered) and amorphous (disordered) material, their orientation to the fiber axis and the size of the crystals present in a fiber. All celluloses, such as cotton, ramie and wood, have the same polymer and unit cell structures, but the fibers have greatly different properties.[23] The differences are due to differences in the orientation of the crystalline and amorphous regions with respect to the fiber axis, in the size and perfection of the crystalline regions, in the relative amounts of crystalline and amorphous materials, and in amounts and type of non-cellulosic material.[23] Corn fibers vary considerably in these parameters relative to the other most common natural fibers as seen from Table 2 and Fig. 1. In comparison to commercially available cotton, linen, and jute fibers, corn fibers have a lower percentage of crystallinity, lower orientation with respect to the fiber's axis, and smaller crystal size.

Table 2 Crystallinity and crystal size in fibers

Fiber	Crystallinity (%)	Crystal size/nm
Corn	**48–50**	**3.2**
Cotton	65–75	5.5
Linen	65–70	2.8
Jute	65–70	2.8

Data for cotton, linen and jute fibers are from refs 7, 21 and 22.

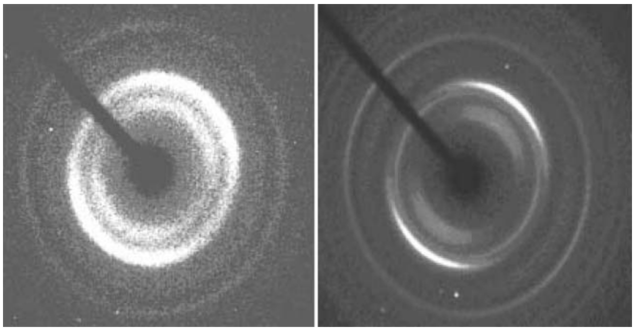

Fig. 1 X-Ray diffraction patterns of corn fiber (left) showing poor orientation of the crystal regions in comparison to cotton (right).

Lower percent crystallinity means, of course, less strength, but also increased elongation, higher moisture regain and more available sites for chemical reactions.[24] The amorphous regions are the regions responsible for the increased elongation, because when the fiber is stretched, molecules in these regions can align themselves to become more oriented to the fiber axis without rupture. Molecules in crystalline regions cannot move easily, and fibers with large percent crystallinity tend to be brittle. Amorphous regions with lots of void space between molecules are also easily accessible to water and chemicals. Therefore corn fibers have higher moisture regain than cotton and would have more easily accessible sites for reactions with dyes and other chemicals as well as greater pliability and elongation.[21]

In addition to crystallinity, the size of crystals also influences the ability of a fiber to absorb water (moisture regain) or other chemicals. Smaller crystal size means more surface area of the fiber and therefore higher accessibility to water and other chemicals. Smaller crystals decrease the distance between layers of cellulose, increasing the capillary effect that brings higher moisture and other chemical absorptions.[21]

Fiber strength, however, is partly determined by the orientation of the crystalline regions to the fiber axis. The orientation of crystals in the fiber is determined from their X-ray diffraction patterns, commonly called fiber diagrams. The fiber diagram of corn fiber shows diffraction arcs much longer and broader than those in cotton, indicating poor orientation of the crystals to the fiber axis as shown in Fig. 1. In addition, the broadening of the arcs in corn fibers along the radius of the pattern is a characteristic of crystallites that are either very small or very imperfect.[22] The lower degree of orientation means fibers that exhibit less strength, because the stress placed upon the fibers may not be in the direction of the strong crystalline regions.

The lower crystallinity and crystal orientation *i.e.* higher amorphous regions of cellulose in cornhusk is what gives corn fibers lower strength than the three most popular cellulosic fibers but corn fibers have increased elongation, higher moisture regain, and more accessible sites for dyes and other chemicals.

Morphological structure

Individual cells in cornhusk are ribbon-like and twisted along their length with periodic reversal in the direction of twists, much like the structure of cotton. These natural convolutions increase the fiber-to-fiber contact and improve the cohesiveness, a desired property for spinning of fibers.[25] Fig. 2a shows an individual cell in cornhusk with a smooth and clean surface since most of the binding materials have been removed, but it is too short to be used for textile and many other applications.

Fig. 2b shows the surface of an untreated cornhusk strand (mechanically removed from the husk) that has a thick layer of protective material and cellular deposits. Individual cells are held together by lignin, hemicellulose, pectin and other binding materials inside this layer. A chemical or mechanical

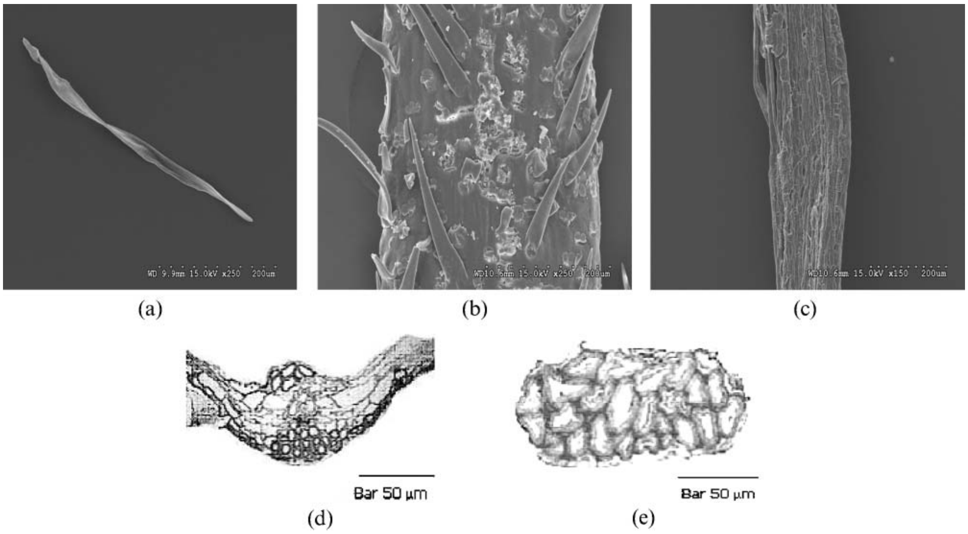

Fig. 2 (a) SEM picture of a unit cell of cellulose in cornhusk obtained by maceration. (b) SEM picture of a strand mechanically extracted from the cornhusk showing the thick deposits on the surface. (c) SEM picture of a fiber obtained after the chemical and enzyme treatments shows unit cells held together by the lignin and other substances. (d) Cross-section of a cornhusk showing vascular bundle of fibers. (e) Cross-section of a fiber bundle obtained using a light microscope.

pre-treatment to break down this protective layer is necessary to obtain fibers with desired properties. The fibers obtained after the alkali and enzyme treatment have an irregular and thin surface as seen in Fig. 2c. It is the extent of removal of these binding materials that determines the fineness, structure and properties of multicellular natural cellulose fibers.[26]

The cross-section of cornhusk without any treatment shows vascular bundles of fibers within encrusting substances such as lignin, hemicellulose, and pectin. During fiber extraction, most of the non-cellulosic substances are removed but the vascular fiber bundles are retained.[11,27] Varying the extraction conditions can alter the width of the fiber bundles. An interesting feature of the fiber cells in cornhusks is the presence of a large lumen, larger than the width of the cell wall in most cells, reducing the density and perhaps increasing the absorbency of the fibers.

The chemical, physical and morphological structures of corn fibers are similar to the most common natural cellulosic fibers, cotton, linen and jute. Due to their smaller crystal size, lower percent crystallinity, and lower orientation, however, corn fibers will be expected to have less strength but are expected to be superior in other properties like durability, dyeability, pliability, and elongation.

Fiber properties

The fiber properties, like strength, elongation, modulus, and moisture regain, are measurable properties that are used to help compare one fiber's performance with another. Fiber properties are determined by fiber structure, but fiber properties provide more meaningful physical comparisons between fibers than do fiber structure comparisons.[22] Often, fiber properties are unique, and that uniqueness is used in combination with other fibers to create materials with the best properties for a particular application.

Tensile properties

Tensile tests measure the behavior of fibers when a force of deformation is applied along the fiber axis in terms of tenacity, % elongation, initial modulus and work of rupture. Tenacity is defined as the specific stress corresponding with the maximum force on a force–extension curve and indicates the load that a fiber can bear before it breaks. Generally, natural fibers have a characteristic higher tenacity and lower elongation or *vice-versa*. The tensile behavior of the fibers in terms of modulus and work of rupture are obtained from the stress–strain curves shown in Fig. 3, the curves for cotton, linen and jute are from the data in literature.[28] Modulus of a fiber measures the slope of the force elongation curve and is a measure of the stiffness of the material, that is its resistance to extension. The higher the modulus of a material, the less it extends for a given force. Cotton has lower modulus than linen and jute and is therefore more flexible and soft. Work of rupture is a measure of the toughness of the material and is the total energy required to break the material and depends on both the tenacity and elongation of a fiber. Higher work of rupture means a more durable fabric even though the fiber has low strength. For example, although wool has lower tenacity than cotton, it is more durable due to its high elongation and therefore higher work of rupture. Jute has low work of rupture and hence is less durable than linen and cotton.

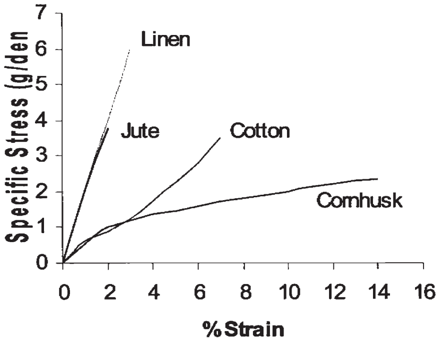

Fig. 3 Stress–strain curve for fibers.

Corn fiber has the unique advantage of moderate strength but with higher toughness, low modulus and higher elongation as reported in Table 3. These properties make it highly durable but pliable and soft, a property desired for apparel and similar applications. The work of rupture for corn fibers is higher than cotton, however, so that though weaker, corn fiber is tougher or more durable to wear. Therefore, with the unique and exceptional blend of moderate strength, high elongation, great pliability and toughness, corn fibers are ideal for all practical applications utilizing natural fibers.

Moisture sorption properties

The higher moisture regain of corn fibers in comparison to cotton is due to the lower crystallinity and crystal size of cellulose in corn fibers. As predicted by chemical and physical structure, the higher amount of accessible regions, surface area and capillary effect contribute to the higher regain of corn fibers. Although linen and jute fibers have higher crystallinity than corn fibers, their relatively higher moisture regain is due to the presence of non-cellulosic substances, especially hemicellulose and pectin, which are hydrophilic.[29,30] The high moisture regain of corn fibers suggests that apparel made from corn fibers would be comfortable to wear. The unique corn fiber properties compare favorably with those of other

Table 3 Comparison of the tensile properties of cornhusk fibers with cotton, linen and jute

Fiber	Tenacity/g den^{-1}	Elongation (%)	Modulus/g den^{-1}	Work of rupture/g den^{-1}	Moisture regain (%)
Corn	**2.7 ± 0.11**	**15.3 ± 2.15**	**70 ± 1.65**	**0.23 ± 0.05**	**9.5**
Cotton	2.7–3.5	6.0–9.0	55	0.19	8.5
Linen	5.8–6.1	2.0–3.0	203	0.09	12.0
Jute	3.2–3.5	0.9–1.2	195	0.03	13.8

Data for cotton, linen and jute fibers are from refs 7, 21 and 22.

common natural cellulosic fibers which make them suitable for use in all fibrous applications.

Effect of bleaching

Bleaching of corn fibers results in removal of the natural yellow color of the fibers, reduction in denier and increase in strength of the fibers. Raw unbleached corn fibers had a YI of 43 whereas the bleached fibers had a WI of 98.

As described earlier, the unit cells in corn fibers are very short, and the fibers are formed by binding these unit cells together with lignin and other binding substances. Therefore, the strength of the corn fibers is partly determined by the binding perfections between the unit cells. The stronger bindings between the unit cells were much less vulnerable than the weaker bindings to the attack by the bleaching agents. Therefore, more weak bindings in the corn fiber were removed during bleaching, resulting in a decrease in denier by about 30% and an increase in strength by about 13%.

Although bleaching eliminates some of the weak bindings in the fiber, it may also damage the cellulose polymers through oxidation. However, the net increase in fiber strength indicates that if the bleaching conditions are well controlled, the damage to the fiber could be minimized.

Conclusions

The structure and properties of corn fibers are similar to the two most common natural cellulose fibers cotton and linen. The unique properties of cornhusk fibers such as good pliability, moderate strength, durability, high elongation, and high moisture regain would provide unique properties to products made from corn fibers. The potential availability of more than 9 million tons of corn fiber every year at a price competitive to the prevailing cotton price will make them attractive to industries utilizing natural fibers and also to consumers. The several benefits possible to agriculture, industrial materials, energy and the environment by using corn fibers are expected to make these fibers preferable over the currently available natural and man-made fibers. Producing food and fiber from the same source without additional need for land or other natural resources will help to satisfy the two basic necessities of the more than 6 billion people on our shrinking earth.

Acknowledgements

This work was financially supported by the Consortium for Plant Biotechnology Research, Inc., University of Nebraska-Lincoln Agricultural Research Division (Journal Series No. 14629) and by Hatch Act. We thank Wenlong Zhou and Wendy Holley for their help in improving the manuscript.

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Recovery of amino acids by imidazolium based ionic liquids from aqueous media

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Received 13th October 2004, Accepted 3rd February 2005
First published as an Advance Article on the web 18th February 2005
DOI: 10.1039/b415842c

In this paper, imidazolium based ionic liquids [C_4mim][PF_6], [C_6mim][PF_6], [C_6mim][BF_4] and [C_8mim][BF_4] were used as alternative solvents for the recovery of some amino acids (L-tryptophan, L-phenylalanine, L-tyrosine, L-leucine and D-valine) from aqueous media. The experimental results shown that logarithm of partition coefficients, log ($P_{IL/W}$), of the amino acids correlate well with the hydrophobicity of the amino acids, indicating the importance of the hydrophobic effect of amino acids as a driving force for their partition into a particular ionic liquid. The partition coefficients are found to be strongly affected by pH of aqueous phases and the water solubility in ionic liquids. They decrease steeply with increasing pH in the range of $pH < pK_1$, but increase with increasing solubility of water in ionic liquid phases. The higher extraction degree at low pHs has been interpreted by the strong electrostatic interactions between cationic form of the amino acids and anion of the ionic liquids. The importance of anionic nature and the alkyl chain length on the cation of ionic liquids have also been examined. It is noted that ionic liquid with BF_4^- anion has much higher extraction efficiency for the amino acids than those with PF_6^- anion because of the stronger effective charge in BF_4^-. It seems likely that there is no correlation between the partition coefficients of the amino acids and the polarity of the ionic liquids. Preliminary results indicated that [C_6mim][BF_4] and [C_8mim][BF_4] ionic liquids may be adapted to liquid-liquid recovery process of some amino acids from aqueous media, and L-tryptophan can be effectively separated from fermentation broth in a multiple step process using [C_6mim][BF_4] as an extractant.

Introduction

Room temperature ionic liquids (ILs) are, as their name implies, liquid ionic media at room temperature resulting from combinations of organic cations and various anions. They have many of the properties of conventional organic solvents, such as excellent solvation qualities and a wide temperature range over which they are liquids. It is reported that ILs are able to dissolve a wide range of species including organic, inorganic and organometallic compounds.[1] Interestingly, one property they don't share with conventional organic solvents is that they have undetectable vapor pressure and high thermal stability. Therefore, room temperature ionic liquids are regarded to be novel environmentally benign solvents in chemical reactions,[1–3] multiphase bioprocess operation,[4] batteries and fuel cells investigations,[5] and they are the basis for at least one industrial process called the BASIL process.[6]

In recent years, ionic liquids have also aroused increasing applications in liquid–liquid extractions of metal ions[7–9] and organic compounds.[10–16] For the pioneer works of using ILs in the liquid-liquid extraction of organic compounds, Rogers and co-workers[10] used 1-n-butyl-3-methylimidazolium hexafluorophosphate [C_4min][PF_6] to study the partitioning of simple, substituted-benzene derivatives between the ionic liquid and aqueous solution. They found that the distribution of these solutes depended on the charged state or relative hydrophobicity of the solutes, those species having charged groups or strong hydrogen bonding moieties (aniline, benzoic acid, *etc.*) have much lower partition coefficients than similar neutral or apolar species (benzene, toluene, *etc.*). A useful correspondence is observed between the distribution of organic solutes in the ionic liquids system and their distribution in an octan-1-ol-water system. They also studied the reversible pH-dependent separations and the fine-tune partitioning behavior of thymol blue into [C_4min][PF_6], 1-n-hexyl-3-methylimidazolium hexafluorophosphate ([C_6min][PF_6]) and 1-n-octyl-3-methylimidazolium hexafluorophosphate ([C_8min][PF_6]) ionic liquids, as well as the solid-liquid separations with low melting ionic liquid 1-n-decyl-3-methylimidazolium hexafluorophosphate [C_{10}min][PF_6].[11] Fadeev and Meagher[12] investigated the recovery of biofuels (butyl alcohol) from fermentation broth by [C_4min][PF_6] and [C_8min][PF_6] ionic liquids, and found that water solubility in ionic liquid and ionic liquid solubility in water are important factors affecting selectivity of butyl alcohol extraction from aqueous solutions. Wasserscheid *et al.*[13,14] explored the possibility of extracting S-compounds from gasoline and diesel oil by ionic liquids. Afonso and co-workers[15,16] obtained an extremely highly selective transport of secondary amines over tertiary amines (up to a 55 : 1 ratio) by using [C_4min][PF_6] ionic liquid as an immobilized phase in a polyvinylidene fluoride supporting membrane.

Separation of bioproducts from the bioreaction media is an important process in biotechnology. Extraction can be applied

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to their crude separation or purification. Amino acids are a class of useful bioproducts for various applications. The conventional separation of amino acids includes the ionic exchange, liquid membrane with extractants,[17] and reversed micelle methods.[18] However, most of these processes use organic solvents that are flammable, hazardous and toxic to humans and microorganisms. Recently, Armstrong and co-workers[19] reported [C_4mim][PF_6]–water distribution coefficients of a set of 40 compounds including three aromatic amino acids. It is found that the partition coefficients ($P_{IL/W}$) values of histidine, phenylalanine and tryptophan at pH = 5.1 were 0.17, 0.013 and 0.012, respectively. Those values at pH = 2 and pH = 10 were so low that they could not be measured accurately. However, with 2.56×10^{-2} mol L^{-1} crown ether (dibenzo-18-crown-6) in the ionic liquid phase, the partition coefficients of phenylalanine and tryptophan at pH = 1.0 was increased to 0.41 and 1.7, respectively. Interestingly, in the presence of 0.05–0.10 mol L^{-1} dicyclohexano-18-crown-6, amino acids glycine, tryptophan, leucine and alanine can be extracted efficiently by [C_4mim][PF_6] from aqueous solution.[20]

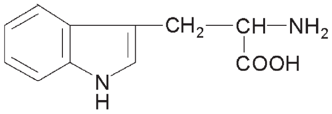
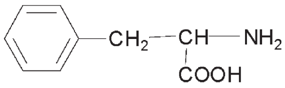
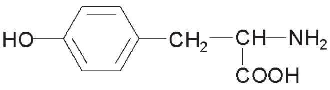
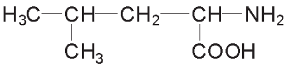
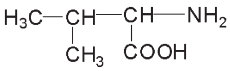
The aim of this work is to determine the factors that control the extraction degree of amino acids from aqueous media, in order to improve the recovery efficiency of amino acids by ionic liquids. For this purpose, extraction equilibrium experiments were performed at different experimental conditions. Five amino acids with different chemical structures (see Table 1) were chosen: valine (Val), leucine (Leu), phenylalanine (Phe), tyrosine (Tyr) and tryptophan (Trp). Using these amino acids, we can examine the effect of –CH_2, –OH, pyrrole ring and the hydrophobicity on the extraction of amino acids. At the same time, [C_4mim][PF_6], [C_6mim][PF_6], [C_6mim][BF_4] and [C_8mim][BF_4] ionic liquids were selected. In this way, it is possible to investigate how the nature of anions, length of the alkyl chains on the imidazolium ring and the polarity of the ionic liquids affect recovery of the amino acids from aqueous media.

Results and discussion

Effect of hydrophobicity of amino acids on the partition coefficients

Data in Tables 2–4 reveal some interesting features for the partition coefficients of the amino acids into a particular ionic liquid at a given pH: (i) aromatic amino acids > aliphatic amino acids; (ii) in aromatic amino acids, Trp > Phe > Tyr; (iii) in aliphatic amino acids, Leu > Val. From chemical structure of the amino acids shown in Table 1, it can be seen that tryptophan and tyrosine have an additional pyrrole ring and an additional –OH group compared respectively with phenylalanine, and leucine has a –CH_2 group more than valine. Pyrrole ring and –CH_2 group are hydrophobic, whereas –OH group is hydrophilic in nature. So it seems appropriate to state that hydrophobic groups increase but hydrophilic groups decrease the partition of the amino acids into a particular ionic liquid at the same pH. In order to further examine this hydrophobic effect, we plotted log ($P_{IL/W}$) against the hydrophobicity scale defined as the free energy change when each amino acid transfers from water to ethanol phase,[22] good correlations were obtained between log ($P_{IL/W}$) and hydrophobicity of these amino acids. Considering the fact that the polarities of these ionic liquids are comparable to that of the lower alcohols,[23] these correlations are understandable. Fig. 1 is a representive plot showing such correlations in [C_6mim][BF_4] at given pHs. It is evident that the extraction degree of amino acids increases with increasing hydrophobicity of amino acids. Similar results were obtained when [C_8mim][BF_4] or [C_4mim][PF_6] were used as extracting phases.

Table 1 Structure of the amino acids and their dissociation constants and solubilities in water at 25 °C

Amino acid	Structure	pK_1	pK_2	pK_3	Solubility/g (100 g^{-1})[a]
Tryptophan		2.38	9.39		1.136
Phenylalanine		2.13	8.62		2.965
Tyrosine		2.20	9.11	10.07	0.045
Leucine	 $H_3C-\underset{CH_3}{CH}-CH_2-\underset{COOH}{CH}-NH_2$	2.36	9.60		2.426
Valine	 $H_3C-\underset{CH_3}{CH}-\underset{COOH}{CH}-NH_2$	2.32	9.62		8.850

[a] Ref. 21.

Table 2 Partition coefficients of the amino acids between [C_6mim][BF_4] and aqueous solutions as a function of the feed pH

Trp				Phe				Tyr				Leu				Val			
pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$
1.00	3.97	0.412	8.64	1.02	2.74	1.25	1.19	0.82	1.78	0.812	1.19	0.90	2.46	1.42	0.732	1.02	3.65	2.29	0.594
1.21	4.07	0.452	8.00	1.50	5.62	2.80	1.01	1.05	2.57	1.24	1.07	1.24	3.05	1.97	0.548	1.21	4.70	3.12	0.506
1.50	4.46	0.593	6.52	1.93	4.75	2.68	0.772	1.41	2.47	1.33	0.857	1.50	3.82	2.54	0.504	1.49	5.12	3.61	0.418
1.94	4.49	0.675	5.65	2.20	4.67	3.09	0.511	1.70	2.63	1.55	0.697	1.70	3.84	2.76	0.391	1.70	5.02	4.04	0.243
2.30	4.51	1.02	3.42	2.50	4.81	3.47	0.386	1.90	2.66	1.73	0.538	1.94	3.82	2.91	0.313	2.00	5.53	4.73	0.169
2.48	4.53	1.10	3.12	2.72	4.67	3.71	0.259	2.11	2.54	1.89	0.344	2.46	4.01	3.50	0.146	2.49	5.75	5.16	0.114
2.96	4.61	1.81	1.55	3.03	4.93	4.18	0.179	2.52	2.57	2.07	0.242	3.00	4.35	4.05	0.074	2.88	5.87	5.58	0.052
3.96	4.65	2.26	1.06	3.96	5.05	4.44	0.137	3.16	2.54	2.33	0.090	4.00	4.54	4.45	0.020	4.00		undetectable	
5.00	4.56	2.15	1.12	5.03	4.69	4.10	0.144	4.10	2.59	2.41	0.075	4.89	3.80	3.76	0.011				
6.10	4.14	2.06	1.01	6.20	4.18	3.82	0.094	5.20	2.63	2.44	0.078	6.10	4.07	4.05	0.005				

Table 3 Partition coefficients of the amino acids between [C_8mim][BF_4] and aqueous solutions as a function of the feed pH

Trp				Phe				Tyr			
pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$
0.94	3.52	0.51	5.90	1.04	3.11	1.77	0.757	0.94	9.55	7.57	0.262
1.08	3.81	0.73	4.22	1.20	3.86	2.42	0.595	1.22	10.5	8.94	0.174
1.20	3.99	0.83	3.81	1.36	4.42	3.17	0.394	1.48	11.0	9.84	0.118
1.45	4.31	1.07	3.03	1.77	4.81	3.78	0.272	1.73	10.8	9.95	0.085
1.72	4.28	1.25	2.42	1.99	4.93	4.02	0.226	1.99	10.7	10.1	0.059
2.00	4.23	1.35	2.13	2.31	5.01	4.44	0.128	2.61	10.6	10.3	0.029
2.53	4.31	1.72	1.51	2.70	5.09	4.60	0.107	3.00		undetectable	
3.01	4.21	1.72	1.45	3.67	5.11	4.65	0.099				
3.88	4.17	1.79	1.33	5.57	5.09	4.85	0.049				
5.77	4.39	1.98	1.22								

Table 4 Partition coefficients of the amino acids between [C_4mim][PF_6] or [C_6mim][PF_6] and aqueous solutions as a function of the feed pH

Trp in [C_4mim][PF_6]				Phe in [C_4mim][PF_6]				Trp in [C_6mim][PF_6]			
pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$	pH	10^3 C_i	10^3 C_f	$P_{IL/W}$
0.94	3.80	2.58	0.473	0.90	3.92	3.35	0.170	0.94	3.47	3.16	0.098
1.25	3.91	2.83	0.382	1.20	4.26	3.80	0.121	1.17	4.17	4.02	0.037
1.48	4.27	3.27	0.306	1.42	3.35	3.03	0.106	1.70	3.81	3.70	0.030
1.76	4.31	3.45	0.249	1.84	4.42	4.08	0.083	2.00	4.83	4.72	0.023
2.00	4.35	3.67	0.185	2.03	4.69	4.36	0.076	2.50	4.99	4.89	0.020
2.40	4.32	3.93	0.099	2.48	4.46	4.32	0.032				
3.06	4.54	4.34	0.046	3.93	4.24	4.12	0.029				
4.16	4.30	4.24	0.014	5.00	4.50	4.40	0.023				

This indicates the importance of hydrophobic effect as a driving force for the extraction of amino acids into ionic liquids.

pH dependence of amino acid distributions

As an example, the effect of the feed pH on the partition coefficients of amino acids into [C_6mim][BF_4] is shown in Fig. 2. It is clearly shown that $P_{IL/W}$ values of the amino acids decrease steeply in the range of pH $<$ pK_1, and an almost plateau was observed under the condition p$K_1 <$ pH $<$ pK_2. Similar results have been found in other ionic liquids investigated. It is well known that the charged characteristics of amino acids are greatly affected by the pH of aqueous solutions. Depending on the pH of the aqueous phase, their hydrophilic groups can be ionized and lead to different equilibrium forms: a cationic form, a zwitterionic form, and an anionic form. The cationic form is predominant in the range of pH $<$ pK_1, but the zwitterionic and the anionic forms are the main forms in the range of p$K_1 <$ pH $<$ pK_2 and pH $>$ pK_2, respectively. As far as the range of pH $<$ pK_1 is concerned, the percentage of the cationic form decreases with increasing pH of the aqueous phase. Therefore, it seems appropriate to state that the decreased percentage of the cationic form of amino acids is responsible for their decreased partition coefficients, shown in Fig. 2. This suggests that electrostatic interactions between the cationic form of the amino acids and the anion of the ionic liquids are important for the extraction process, and the stronger electrostatic interactions are necessary for the higher degree of extraction of the amino acids.

Data analysis indicated that the effect of the feed pH on the partition coefficient of amino acids in ionic liquids (at pH $<$ 5.0) can be correlated by a linear equation:

$$\log (P_{IL/W}) = a + b\,(\text{pH}) \qquad (1)$$

The values of the intercept a and slope b for different ionic liquid–water systems have been obtained by least squares

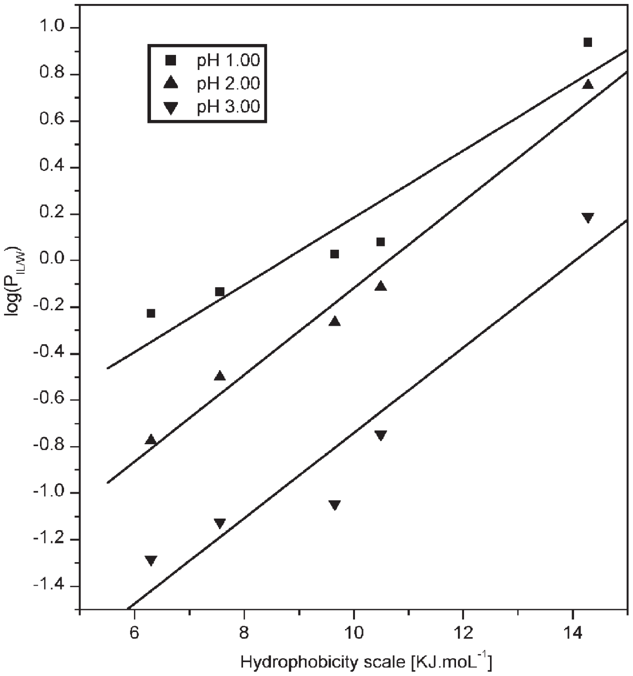


Fig. 1 Relation between partition coefficients into [C$_6$mim][BF$_4$] and hydrophobicity of the amino acids at given pHs.

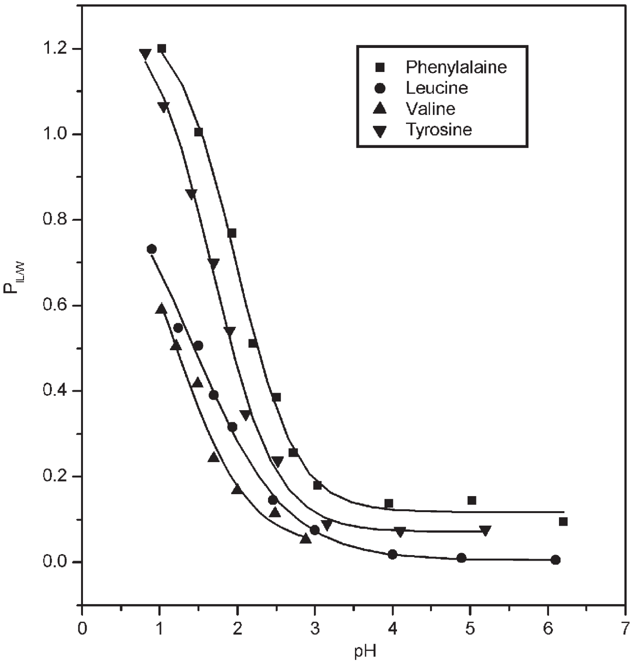


Fig. 2 pH dependence of partition coefficients of the amino acids into [C$_6$mim][BF$_4$].

analysis and are listed in Table 5 together with their correlation coefficients.

Table 5 Values of the intercept *a* and slope *b* in eqn. (1) and the linear correlation coefficients (*r*)

IL	Amino acids	*a*	*b*	*r*
[C$_6$mim][BF$_4$]	Trp	1.309 ± 0.063	−0.336 ± 0.027	−0.982
	Phe	0.500 ± 0.093	−0.368 ± 0.037	−0.971
	Tyr	0.470 ± 0.079	−0.420 ± 0.034	−0.978
	Leu	0.446 ± 0.061	−0.531 ± 0.026	−0.993
	Val	0.378 ± 0.070	−0.560 ± 0.036	−0.990
[C$_8$mim][BF$_4$]	Trp	0.825 ± 0.074	−0.213 ± 0.034	−0.921
	Phe	0.371 ± 0.068	−0.519 ± 0.037	−0.988
	Tyr	−0.105 ± 0.039	−0.539 ± 0.022	−0.997
[C$_4$mim][PF$_6$]	Trp	0.200 ± 0.037	−0.492 ± 0.016	−0.997
	Phe	−0.611 ± 0.032	−0.241 ± 0.015	−0.992
[C$_6$mim][PF$_6$]	Trp	−0.840 ± 0.209	−0.371 ± 0.119	−0.874

Effect of chemical structure of the ionic liquids on the partition coefficients

As can be seen from Tables 2 and 4, partition coefficients of the amino acids into [C$_6$mim][BF$_4$] are much higher than those into [C$_6$mim][PF$_6$] under the same conditions. For example, the $P_{IL/W}$ value of tryptophan into [C$_6$mim][BF$_4$] is nearly 90 times higher than that into [C$_6$mim][PF$_6$] at pH = 1.0. This surprising difference in $P_{IL/W}$ implies that the anion of the ionic liquids plays a key role in the extraction of amino acids. Quantum chemical calculations[24] indicated that the effective negative charge in the BF_4^- anion is much stronger than that in the PF_6^- anion. Therefore, stronger electrostatic interactions between the cationic form of the amino acids and the BF_4^- anion and accordingly a higher extraction degree by BF_4^- based ionic liquids will be expected.

From the partition data of the amino acids into [C$_6$mim][BF$_4$] and [C$_8$mim][BF$_4$] ionic liquids, it is interesting to note that the phase preference for the amino acids decreased as the length of alkyl substituent on the cation increased from C$_6$ to C$_8$. For instance, at pH ≈ 1.0, the partition coefficient of tryptophan is 8.64 into [C$_6$mim][BF$_4$] and 4.22 into [C$_8$mim][BF$_4$], respectively. Similar results are observed in [C$_4$mim][PF$_6$] and [C$_6$mim][PF$_6$] ionic liquids. NMR studies[25,26] show that stronger hydrogen bond associations are formed between the H2 of the imidazolium ring and the fluorine of the anion in [C$_2$mim][BF$_4$], [C$_4$mim][BF$_4$] and [C$_4$mim][PF$_6$] ionic liquids. Considering the fact that the side chain moieties of some amino acids investigated in this work, such as tryptophan, are large in volume, it may be possible that the longer alkyl chain on the imidazolium ring of the cation of ionic liquids has a screening effect or a steric hindrance effect for the electrostatic attractive interactions of the cationic form of the amino acids with the anion of the ionic liquids. In investigations of solute–solvent interactions within binary ionic liquid mixtures, a screening effect of alkyl chain on the imidazolium ring has been suggested by Pandey and co-workers.[27]

The polarity of ionic liquids has been investigated[23,28–31] by using both solvatochromic and fluorescent dyes. It was found that although the polarity of several ionic liquids may be varied over a wide range by attachment of functional group-containing substituents to the imidazolium cation,[31] the range of polarities is small for a huge range of ionic liquids. For the ionic liquids investigated in this work, their polarity follows the trend: [C$_6$mim][BF$_4$] ≈ [C$_6$mim][PF$_6$], [C$_6$mim][BF$_4$] > [C$_8$mim][BF$_4$] and [C$_4$mim][PF$_6$] < [C$_6$mim][PF$_6$]. Based on these results, it seems likely that there is no correlation between the partition coefficients of the amino acids and the polarity of the ionic liquids.

Table 6 Mutual solubilities of ionic liquids with water at ambient conditions

IL	IL in aqueous phase (wt %)	Water in IL phase (wt %)
$[C_4mim][PF_6]$	2.0 ± 0.3^a	2.3 ± 0.2^a
$[C_6mim][PF_6]$	0.75^b	0.88^b
$[C_6mim][BF_4]$	6.7 ± 0.1^c	12.2 ± 0.1^c
$[C_8mim][BF_4]$	1.8 ± 0.5^a	10.8 ± 0.5^a

[a] Ref. 32. [b] Ref. 33. [c] This work.

Effect of water solubility in ionic liquid phases and temperature on the partition of amino acids

Included in Table 6 are the data of mutual solubilities of ionic liquid with water at room temperature. It is clear that the solubility of water in the ionic liquid phases decreases in the order $[C_6mim][BF_4] > [C_8mim][BF_4] > [C_4mim][PF_6] > [C_6mim][PF_6]$. This order is the same as the partition coefficients of the amino acids in these ionic liquids, indicating a possible correlation between these two physicochemical properties. Using ATR and transmission IR spectroscopy, Welton and co-workers[34] investigated the state of water in ionic liquids based on the 1-alkyl-3-methylimidazolium cation with various anions. It has been shown that in these ionic liquids, water molecules are present mostly in the free (not self-associated) state, bound *via* H-bonding with PF_6^-, BF_4^- and other anions in the concentration range of water from 0.2 to 1.0 mol L^{-1}. The water content in ionic liquids and the strength of hydrogen bonds between water molecules and the anions follow the order $BF_4^- > PF_6^-$. Therefore, presence of water is expected to partially disrupt the hydrogen bond association between the cation and the anion of the ionic liquids, leading possibly to an increase in the number of free ions (cation and anion) and the ionic mobility in the ionic liquid phase. This increase would then enhance the electrostatic interactions between the cationic form of the amino acids and the anions of the ionic liquids. Accordingly, partitioning of the amino acids will be preferred in an ionic liquid with higher water solubility.

In order to examine the effect of temperature on the partitioning of the amino acids, the extraction of tryptophan between $[C_6mim][BF_4]$ and aqueous solution was carried out at 15, 25, 35, 45, and 50 °C. Fig. 3 shows the temperature dependence of the partition coefficients. Obviously, the temperature effect is negligible. Therefore we performed the partition experiments at room temperature without worrying about the temperature fluctuations.

Compared with other methods

As indicated by the data in Tables 2 and 3, among the ionic liquids investigated in this work, $[C_6mim][BF_4]$ shows the highest extraction efficiency for tryptophan, phenylalanine, tyrosine and leucine, especially in the low pH range. The extraction degree of tryptophan and phenylalanine by $[C_8mim][BF_4]$ is also acceptable for practical applications. In addition, it should be pointed out that partition coefficients of the amino acids in $[C_6mim][BF_4]$ at low pHs are comparable to those in the AOT–n-heptane microemulsion.[18] Also, we found that at pH = 1.0, the extraction degree of tryptophan in $[C_6mim][BF_4]$ and $[C_8mim][BF_4]$ is, respectively, about 5 and 2.5 times as high as that in a $[C_4mim][PF_6]$ + dibenzo-18-crown-6 system.[19] However, they are much lower than in a $[C_4mim][PF_6]$ + dicyclohexano-18-crown-6 mixture.[20] Huddleston *et al.*[10] noted that even low partition coefficients could result in an economical recovery process due to the non-volatility of the extraction phase. Therefore, $[C_6mim][BF_4]$ and $[C_8mim][BF_4]$ ionic liquids may be adapted to a liquid–liquid recovery process of some amino acids from aqueous media.

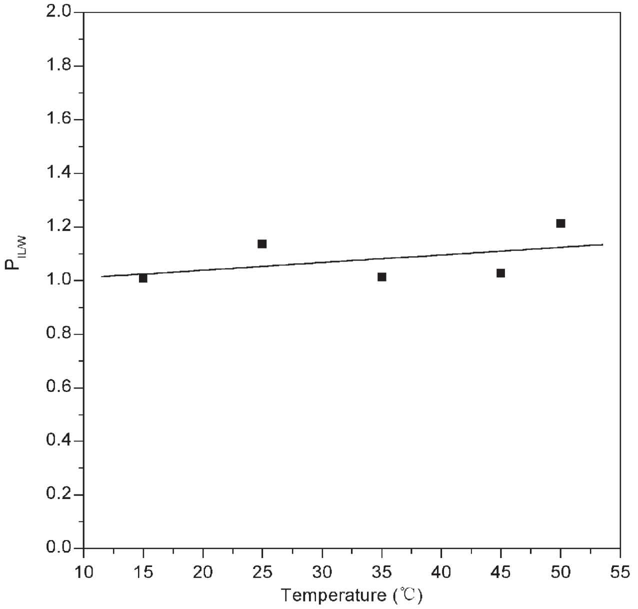


Fig. 3 Effect of temperature on the partition coefficients of tryptophan into $[C_6mim][BF_4]$.

Selective extraction of L-tryptophan from the mixture of amino acids

L-Phe and L-Tyr are the main impurity source of amino acids in L-Trp fermentation broth. In order to illustrate the possibility of the selective separation of L-Trp by ionic liquids, we determined the distribution ratios of the amino acid in L-Trp + L-Phe, L-Trp + L-Tyr and L-Trp + L-Phe + L-Tyr mixtures between $[C_6mim][BF_4]$ and aqueous solutions. The results indicate that in L-Trp + L-Phe + L-Tyr mixtures, the $P_{IL/W}$ values for L-Trp, L-Phe and L-Tyr are 3.250, 0.428 and 0.141, respectively. The selective ratio is 7.59 for L-Trp to L-Phe, 23.05 for L-Trp to L-Tyr. In L-Trp + L-Phe and L-Trp + L-Tyr mixtures, the corresponding selective ratios of these amino acids are 4.75 and 34.34, respectively. These findings indicate that L-Trp can be effectively separated from fermentation broth in a multiple step process using $[C_6mim][BF_4]$ as an extracting agent.

Conclusions

From the above discussions, it can be concluded tentatively that the hydrophobicity effect of the amino acids is a driving force for their recovery into the ionic liquids. The partition coefficients of the amino acids are influenced greatly by the pH of the aqueous phase. This effect can be modeled by a linear equation between log ($P_{IL/W}$) and pH in the range of pH < 5.0. The electrostatic interactions between the cation form of the amino acids and the anion of the ionic liquids are suggested to be responsible for the higher degree of extraction in the low pH range. It is found that the ionic liquids with BF_4^- as anion are a much better extraction phase than the corresponding ionic liquids with PF_6^- as anion under the same conditions. The extraction degree of the amino acids decreases with increasing length of alkyl substituent chain on the cation of the ionic liquids, but it increases with increasing solubility of water in ionic liquid phases. However, no correlation was observed between the partition coefficients of the amino acids and the polarity of the ionic liquids. Among the ionic liquids investigated, the extraction degree of some of the amino acids by [C_6mim][BF_4] and [C_8mim][BF_4] may be acceptable for practical applications, and L-Trp can be effectively extracted from L-Phe, L-Tyr and their mixtures in a multiple step process using [C_6mim][BF_4] as an extractant. Therefore, the structure of ions in ionic liquids can be designed to meet the needs of a practical extraction process for amino acids.

Experimental

Reagents

1-Bromobutane, 1-bromohexane, 1-bromooctane and 1-methylimidazolium (Shanghai Chem. Co., C. P.) were distilled twice at reduced pressure. The middle fraction of the distillate was collected. Sodium hexafluorophosphate $NaPF_6$ and sodium tetrafluoroborate $NaBF_4$ (Shanghai Chem. Co., C. P.) were purified by recrystallization twice from deionized water. L-Tryptophan, L-phenylalanine, L-leucine, D-valine and L-tyrosine (Shanghai Chem. Co., B. R.) were used without further purification. Ninhydrine (Tianjin kemio. Co., A. R.) was also used as received. Hydrochloric acid and sodium hydroxide (Shanghai Chem. Co., A. R., 1 M solutions) were used to adjust the pH of aqueous solutions. Water was freshly deionized and distilled before use.

Preparation of ionic liquids

[C_4mim][PF_6], [C_6mim][PF_6], [C_6mim][BF_4] and [C_8mim][BF_4] ionic liquids were synthesized as described by Bonhote and co-workers.[35] Briefly, 208 g (1.518 mol) of freshly distilled bromobutane was added dropwise over 1 h into vigorously stirring solution of 126 g (1.518 mol) 1-methylimidazolium dissolved in 200 ml of 1,1,1-trichloroethane. The mixture, already turbid, was refluxed for 12 h. The 1-butyl-3-methylimidazolium bromide was decanted from the hot solution in a separatory funnel, washed twice with 200 ml of trichloroethane, and dried on a rotavapor at 70 °C under reduced pressure.

$NaPF_6$ (1.364 mol) aqueous solution was added slowly to a magnetically stirred solution of 1-butyl-3-methylimidazolium bromide (300 g, 1.364 mol) dissolved in 100 ml water in a plastic bottle cooled in an ice bath. When the addition was completed, the mixture was stirred for 12 h, and then poured into separatory funnel and the two layers were separated. The organic layer was dissolved in dichloromethane and deionized water was then added. After vigorous stirring, the water layer was replaced with 20 ml of fresh deionized water. This procedure was repeated until no precipitation of AgBr occurred in the aqueous phase on addition of a concentrated $AgNO_3$ solution. The solvent in the organic phase was removed *in vacuo* and the resulting ionic liquid [C_4mim][PF_6] was collected. The yield was about 60%. The same procedure was applied for the preparation of [C_6mim][PF_6], [C_6mim][BF_4] and [C_8mim][BF_4] ionic liquids.

Partition coefficient measurements

The IL/water partition coefficients of the amino acids were determined at room temperature (20 ± 0.5 °C). 1.0 ml aqueous solution of amino acid was contacted with 1.0 ml of pure IL. The phase-contacting experiments were carried out in carefully stoppered 16 × 75 mm glass test tubes. The system was vigorously stirred with magnetic stirrer. After stirring for 30 minutes, the two phases were carefully separated using a centrifuge.

The pH of the aqueous phase was measured with an Orion pH meter (model 720) using a combination pH electrode. Before and after extraction, concentrations of Trp and Tyr in aqueous solutions were determined with a Shanghai UV spectrophotometer (model 752), and those of Phe, Leu and Val were determined by the ninhydrine method.[36] For mixtures of the amino acids, their concentrations were measured by liquid chromatography using an Agilent liquid chromatograph (HP 1100) equipped with an UV detector. The partition coefficients of amino acids between the IL and aqueous solution were calculated by:

$$P_{IL/W} = (C_i - C_f)/C_f \qquad (2)$$

where C_i and C_f refer to the initial and final concentrations (mol L^{-1}) of any given amino acids in aqueous phases, respectively. The experimental partition coefficient values were listed in Tables 2–4 as a function of pH for aqueous solutions. The values of $P_{IL/W}$ were measured in duplicate with uncertainty within 5%. Because of the limited solubilities of some amino acids in [C_8mim][BF_4], [C_4mim][PF_6] and [C_6mim][PF_6] ionic liquids, only accurate partition data of tryptophan, phenylalanine and tyrosine into [C_8mim][BF_4], of tryptophan and phenylalanine into [C_4mim][PF_6], and tryptophan into [C_6mim][PF_6] were obtained.

IL/water mutual solubility measurements

For the measurements of IL/water mutual solubilities, the procedure described by Brennecke and co-workers[32] has been closely followed. 5 ml of [C_6mim][BF_4] and 5 ml of water were vigorously mixed in a test tube immersed in a water bath that was controlled to 22 ± 0.1 °C. The phases were allowed to separate for 1 to 2 h after cessation of the stirring in order to ensure clean separation for the phases. The IL content in the water-rich phase was analyzed with a Shanghai UV spectrophotometer (model 752). The maximum absorbance is at 211 nm. The water content in the IL-rich phase was determined using a Shanghai Karl Fischer titrator (model ZSD-2).

Acknowledgements

We wish to acknowledge the financial support from the National Natural Science Foundation of China (Grant No. 20273019) and the Innovation Foundation of Henan Education Department.

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Gadolinium triflate immobilized in imidazolium based ionic liquids: a recyclable catalyst and green solvent for acetylation of alcohols and amines

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Received 25th October 2004, Accepted 10th January 2005
First published as an Advance Article on the web 31st January 2005
DOI: 10.1039/b416359a

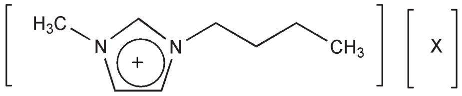
Gadolinium triflate immobilized in room temperature ionic liquids (RTIL) 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) was found to be a recyclable and green catalyst for acetylation of a variety of alcohols, phenols and amines. Acetylation reactions using acetic anhydride (Ac_2O) as the reagent proceeded in excellent yields in the presence of catalytic amounts (0.2–0.5 mol%) of $Gd(OTf)_3$ immobilized in RTILs, at ambient temperature. In addition, the catalyst system $Gd(OTf)_3$/[bmim][X] can be recovered and reused efficiently in these transformations.

Introduction

Acetylation reactions catalyzed by Lewis acids are of enormous interest and used extensively in organic synthesis.[1] Although a number of acid- and base- catalyzed acetylation reactions are known, many of them are limited in their applications either due to the instability of reactants or products under the reaction conditions or tedious workup procedures involved.[2–5]

A variety of Lewis-acid catalyzed acylations of alcohols and amines with acid anhydrides have been explored. Despite a number of methods currently available, new and efficient methods are still in strong demand. Lewis acids such as scandium triflate ($Sc(OTf)_3$),[6] magnesium bromide ($MgBr_2$),[7] tantalum chloride ($TaCl_5$),[8] trimethylsilyl triflate (Me_3SiOTf),[9] copper(II) triflate ($Cu(OTf)_2$),[10] indium triflate ($In(OTf)_3$)[11] and bismuth triflate ($Bi(OTf)_3$)[12,13] have been used as catalysts for these transformations. Most of these metal triflates are either too expensive or water-sensitive. Further, trimethylsilyl triflate is sensitive towards moisture, and is strongly acidic and cannot be used for the acylation of acid-sensitive alcohols. In 1994, Kobayashi and Hachiya used $Gd(OTf)_3$ as a water-tolerant Lewis acid in the aldol reactions of silyl enol ethers with aldehydes, in aqueous media.[14] As part of our interest in the Lewis-acid catalyzed reactions we have recently reported the applications of $Gd(OTf)_3$ as a mild and inexpensive reagent for the acetylation of alcohols and amines.[15]

From the viewpoint of today's environmental consciousness, development of environmentally benign reaction media for organic transformations is crucial. Room temperature ionic liquids (RTILs) that are air and moisture stable have recently been found to be excellent environmentally benign solvents for a variety of reactions such as esterification,[16] Diels–Alder[17], Wittig[18], Suzuki[19] and Heck reactions.[20] Since these RTILs have the advantage of being non volatile, non flammable, and recyclable they offer an alternative to conventional organic solvents. Deng and co-workers reported the application of an RTIL, 1-butylpyridinium chloride-aluminium(III) chloride, as a catalyst and reaction medium for the acylation of alcohols with acetic acid.[21] Recently imidazolium based RTILs have been used as solvents for DCC/DMAP promoted esterification of ferrocenemonocarboxylic acid,[22] and for the acetylation of alcohols in the presence of Lewis acids, $Cu(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $HfCl_4(THF)_2$, and $InCl_3$.[23] As part of our ongoing study of Lewis-acid catalyzed reactions and ionic liquids, we have explored the recyclability of $Gd(OTf)_3$ catalyst in RTILs, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4^-];**1**), and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6^-]; **2**)



1; X = BF_4^-
2; X = PF_6^-

Results and discussion

$Gd(OTf)_3$ is relatively more water tolerant than other lanthanide based metal triflates.[14] Thus strictly anhydrous reaction conditions that have been used with other Lewis acid catalysts can be avoided in the case of this catalyst. In addition, it is a relatively inexpensive reagent. We have recently used this catalyst for efficient and convenient acetylations of alcohols and amines using Ac_2O as the reagent in conventional organic solvents. A variety of primary, secondary and tertiary alcohols as well as phenols and amines can be acylated readily using this water-tolerant Lewis acid.[15]

As RTILs such as [bmim][BF_4] are relatively hygroscopic, we have selected $Gd(OTf)_3$, a water-tolerant Lewis acid, as an immobilizable Lewis acid catalyst in these media. The combination of the environmentally benign nature of the RTILs and recyclability of the catalyst should make the present catalyst system attractive. To examine the catalytic activity of

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$Gd(OTf)_3$ in RTILs, acetylation of benzyl alcohol with Ac_2O was chosen initially as a model reaction. Benzyl alcohol reacted with Ac_2O at room temperature in [bmim][BF_4] and [bmim][PF_6] in the presence of 0.5 mol percent of the catalyst. In [bmim][BF_4] the yields are good to excellent, whereas in [bmim][PF_6] relatively lower yields were obtained. When the solvent–catalyst system is recycled and reused, the catalytic activity was slightly decreased in the case of [bmim][BF_4] (Table 1), whereas a drastic decrease of catalytic activity was observed in the case of [bmim][PF_6] (Table 1).

After having optimized the reaction conditions for benzyl alcohol, acetylations of various alcohols with Ac_2O have been carried out in [bmim][BF_4] in the presence of 0.5 mol% of $Gd(OTf)_3$ as a catalyst at room temperature. The reactions of a variety of alcohols, phenols, diols as well as allylic alcohols proceeded in excellent yields with as low a concentration as 0.2 mol percent of $Gd(OTf)_3$ (Table 2).

We have also investigated the acetylation of amines using $Gd(OTf)_3$ as the catalyst in [bmim][BF_4]. Using as low as 0.2 mol% of the catalyst we have obtained high yields of *N*-acetylated products (Table 3). $Gd(OTf)_3$ catalyzed acetylation of amines proceeded in relatively shorter times as compared to acetylation alcohols as was also observed in case of CH_3CN as the solvent.[15]

For selected compounds in Tables 2 and 3 we have demonstrated recyclability and reuse of the $Gd(OTf)_3$–[bmim][BF_4] catalyst system (Table 4). Moderate to high yields of the products were obtained in second and third runs.

In order to gain insight into the mechanism of these acetylation reactions we have recorded a broad-band ^1H decoupled ^{13}C NMR spectrum for a solution of $Gd(OTf)_3$, Ac_2O and [bmim][BF_4] (1 : 30 : 7 mol ratio). A weak absorption at $\delta^{13}C$ 183.9 (CD_2Cl_2 solvent) was observed indicating the formation of AcOTf as the reactive acylating agent.[15,24] Based on this observation, a schematic representation of the proposed mechanism is shown in Fig. 1.

Experimental

General remarks

Gadolinium triflate and other chemicals used in this study were purchased from Aldrich chemical company and were used as received. All reactions were carried out in air at ambient temperature in oven-dried glassware. Thin layer

Table 1 Acetylation of benzyl alcohol with acetic anhydride using $Gd(OTf)_3$/[bmim][X]

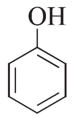
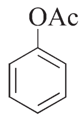
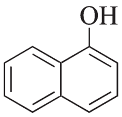
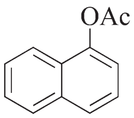
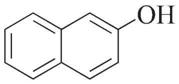
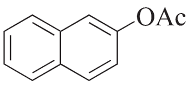
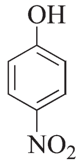
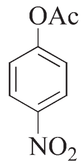
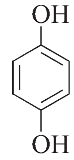
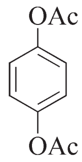
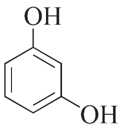
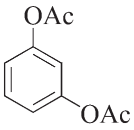
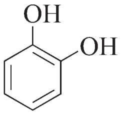
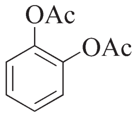
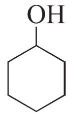
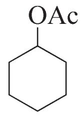
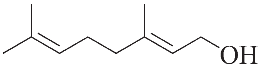
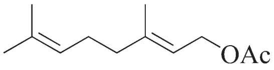
$$PhCH_2OH + Ac_2O \xrightarrow[\text{[bmim][X], RT}]{Gd(OTf)_3(0.5\text{ mol \%})} PhCH_2OAc$$

Entry	[X]	Run	Time/h	Yield (%)[a]
1	BF_4	First	1	92
		Second	1	89
		Third	2	72[b]
2	PF_6	First	4	76
		Second	4	69[b]
		Third	4	40[b]

[a] Isolated yields. [b] Yields estimated by GC-MS.

Table 2 $Gd(OTf)_3$–[bmim][BF_4] catalyzed acetylation of alcohols

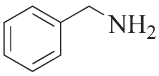
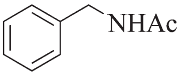
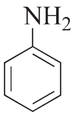
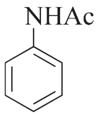
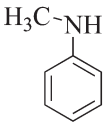
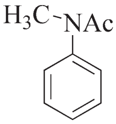
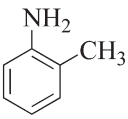
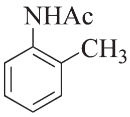
$$R - OH + Ac_2O \xrightarrow[\text{[bmim][BF}_4\text{], RT}]{Gd(OTf)_3(0.5\text{ mol \%})} R - OAc$$

Entry	Alcohol	Product	Yield (%)[a]
1			88
2			92
3			90
4			76
5			99[b]
6			93
7			95
8			92
9			86

[a] Isolated yields. [b] Reaction is carried out with 0.2 mol% of catalyst.

Table 3 Gd(OTf)$_3$ catalyzed acetylation of amines in [bmim][BF$_4$]

$$R-NH_2+Ac_2O \xrightarrow[\text{[bmim][BF}_4\text{], RT}]{\text{Gd(OTf)}_3\text{(0.2 mol \%)}} R-NHAc$$

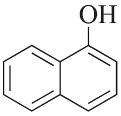
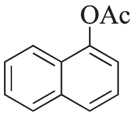
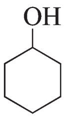
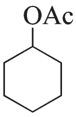
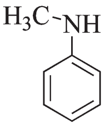
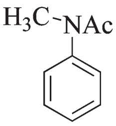
Entry	Amine	Product	Yield (%)[a]
1			90
2			96
3			86
4			89

[a] Isolated yields.

Table 4 Recyclability and reuse of Gd(OTf)$_3$–[bmim][BF$_4$] for representative acetylation reactions

$$R-XH+Ac_2O \xrightarrow[\text{[bmim][BF}_4\text{], RT}]{\text{Gd(OTf)}_3\text{(0.5 mol \%)}} R-XAc$$

$X = O, NH$

Entry	Substrate	Product	Yield (%)[a,b]
1			92 (1st run) 83 (2nd run) 46 (3rd run)
2			92 (1st run) 87 (2nd run) 82 (3rd run)
3			86 (1st run) 78 (2nd run) 72 (3rd run)

[a] Isolated yields. [b] 0.2 mol% of Gd(OTf)$_3$ was used for entry 3.

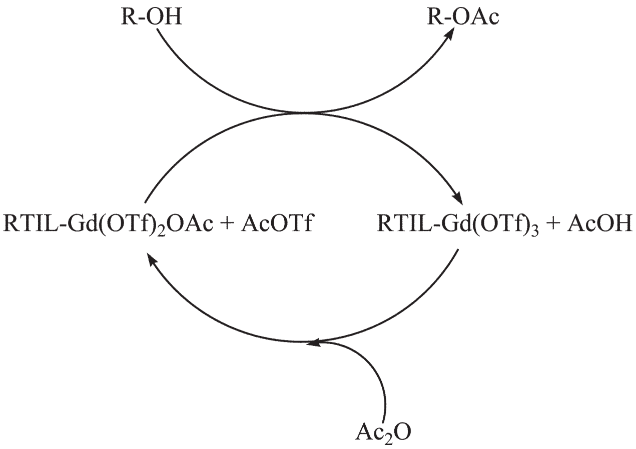


Fig. 1 Schematic representation of the catalytic cycle for RTIL–Gd(OTf)$_3$ catalyzed acetylations.

chromatography was carried out using silica gel coated polyester backed sheets. GC-MS spectra were recorded on Hewlett-Packard 5989A spectrometer, equipped with a Hewlett-Packard 5890 gas chromatograph. ^{1}H NMR and ^{13}C NMR spectra for CDCl$_3$ solutions were recorded on a INOVA-Varian 400 MHz spectrometer at 400 MHz and 100 MHz, respectively, and the chemical shifts are referenced with respect to internal TMS (δ = 0.0).

Synthesis of [bmim][X]

RTILs ([bmim][X]) were prepared by anion exchange of [bmim][Cl] using 1 mol equivalent of NaBF$_4$ or NaPF$_6$.[25] The RTILs were dried under vacuum for 12 h and stored under an atmosphere of dry argon.

General acetylation procedure

A mixture of benzyl alcohol (2.00 g, 18.5 mmol) and Ac$_2$O (2.26 g, 27.5 mmol) was added to [bmim][X] (4 mL) containing Gd(OTf)$_3$ (55 mg, 0.093 mmol, 0.5 mol%). The reaction mixture was stirred at room temperature and the progress of the reaction monitored by TLC. Upon completion of the reaction (30 min to 2 h) diethyl ether (20 mL) was added to the contents and stirred. The supernatant ether layer containing the product was decanted, washed with water, aqueous NaHCO$_3$, brine (20 mL), and dried (Na$_2$SO$_4$) and the solvent was removed on a rotary evaporator to give benzyl acetate. ^{1}H and ^{13}C NMR, and GC-MS of the products are in agreement with the literature data.

The RTIL–Gd(OTf)$_3$ system was dried for 1 h under vacuum and recycled for subsequent runs for reactions shown in Tables 1 and 4.

Conclusions

In conclusion, Gd(OTf)$_3$ immobilized in RTILs is an efficient recyclable catalyst system for acetylation of aliphatic and aromatic alcohols and amines. A variety of alcohols, phenols, diols as well as allylic alcohols and amines have been acetylated using 0.2 mol percent of the catalyst in these environmentally benign solvents. Although the catalytic activity of the recovered catalyst is decreased slightly upon recycling, this method offers a good catalyst system in the context of "green" chemistry.

Acknowledgements

Support of our work by the donors of the American Chemical Society Petroleum Research Fund (PRF No. 39643-AC) is gratefully acknowledged.

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Solid-state regio- and stereo-selective benzylic bromination of diquinoline compounds using *N*-bromosuccinimide

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Received 25th October 2004, Accepted 10th January 2005
First published as an Advance Article on the web 31st January 2005
DOI: 10.1039/b416275g

Solvent-free *N*-bromosuccinimide (NBS) bromination of diquinoline derivatives reveals that benzylic bromination takes place in a regio- and stereo-selective manner in the absence of toxic and ozone-depleting CCl_4 solvent.

The Wohl–Ziegler reaction, namely allylic or benzylic free radical bromination using *N*-bromosuccinimide (NBS) in a refluxing aprotic solvent, is a well-established synthetic organic procedure.[1] Benzene, chloroform, and petrol have been employed as solvents, but the traditional choice has been carbon tetrachloride which combines optimum properties of solubility, reaction temperature, and ease of product isolation. The succinimide by-product can be removed simply by filtration of the cooled reaction mixture, and then evaporation of solvent from the filtrate affords the brominated product.[2] Unfortunately, carbon tetrachloride is an ozone-depleting substance, the supply of which is now controlled under the Montreal Protocol. Consequently, its import and export is banned in many countries. Even if an essential user's licence is granted, the cost may be prohibitive for use as a solvent. It is therefore important to explore alternative conditions applicable to NBS bromination reactions.

Recently, we have synthesised a series of new brominated diquinoline lattice inclusion hosts,[3] some of which have potential in separation chemistry due to their selective properties.[4] In each case, the final step involved a regio- and stereo-selective benzylic NBS bromination in refluxing CCl_4. We now report that identical products can be obtained by means of solid-state reaction.

The dibromide **2** was obtained as a single product after 6 hours mechanical grinding of the parent diquinoline derivative **1** (60 mg, 0.195 mmol) and NBS (120 mg, 0.674 mmol) (Scheme 1). The progress of the reaction was checked at intervals using TLC. Only the starting materials were visible up till 4 hours of grinding, but multiple spots indicated a mixture of compounds after 5 hours. Grinding was stopped at 6 hours when only one major spot (with a different R_f value to **1**) was present.

Reaction was also monitored by ^{1}H NMR spectroscopy, which confirmed the complex composition at 5 hours as being due to the presence of **1**, the mono-bromide, and the dibromide **2**. During the reaction, the aliphatic ABX system of **1** progressively disappeared and was replaced by the AX system of **2**. The aliphatic CH (δ 4.77) and CHBr (δ 6.22) protons of product **2** appear as broad singlets after 6 hours (Fig. 1).

The crude product was mixed with a small volume of acetone and the soluble material decanted onto a flash chromatography column, then eluted to obtain pure **2** in 85% yield. If grinding was continued beyond the optimum time, then the

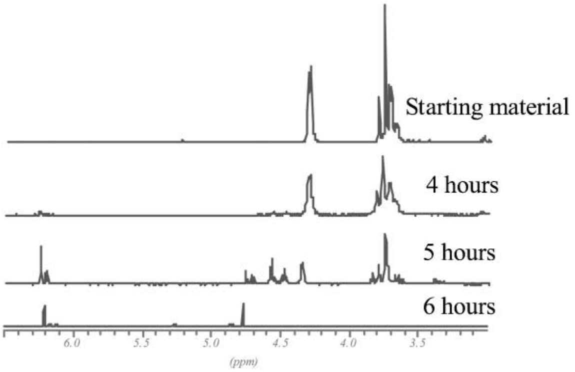

Fig. 1 Progress of the reaction of compound **2** monitored by ^{1}H NMR spectroscopy. Only aliphatic signals are represented however aromatic and succinimide peaks are ignored for clarity.

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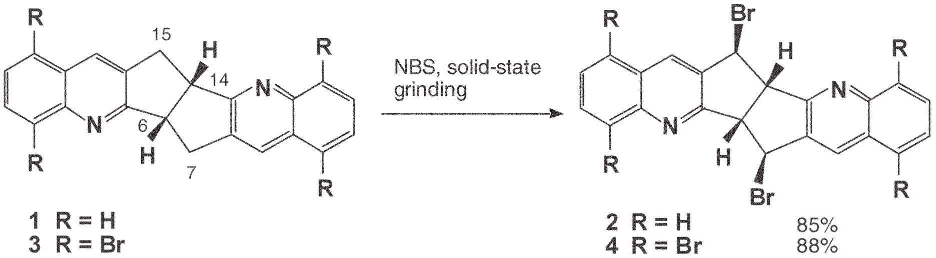

Scheme 1

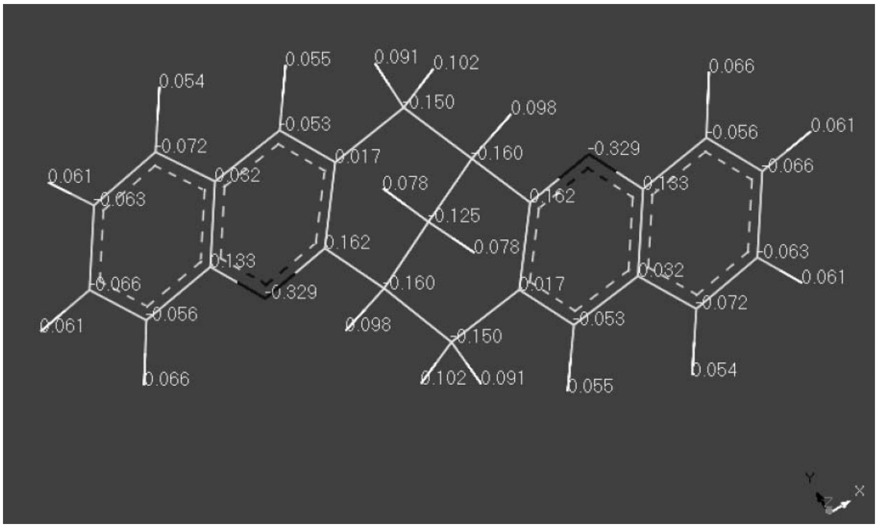

Fig. 2 *Ab initio* calculation for compound **1**.

yield decreased. However, a larger scale reaction using NBS (0.50 g) required an optimum time of 8 hours grinding and gave a comparable yield. The product of these reactions was identical in all respects to that obtained earlier using the CCl_4 method (78%).[4b] Similar solid-state reaction of tetrabromide **3** yielded the hexabromide **4** in 88% yield (CCl_4 method 85%).[4c]

Many solid-state reactions have been explored recently,[5] but these examples are the first reported where the use of solvent-free NBS resulted in benzylic bromination, as opposed to aromatic substitution.[6,7] Goud and Desiraju[6] found that solid-state reactions of NBS with phenols invariably led to nuclear bromination, even for methyl-substituted phenols where competition was possible between the two processes. Aromatic substitution of alkyl aromatics (such as 2-methylnaphthalene) can also dominate if impure NBS is used in the CCl_4 solution reaction.[8] Our use here of π-deficient heterocyclic systems favours the benzylic radical reaction.

Unusually, benzylic bromination of the diquinolines **1** or **3** is both a regio- and stereo-selective process. There are two benzylic sites at which reaction could occur, namely the secondary C7/C15 and the tertiary C6/C14 positions. The initial free radical hydrogen abstraction step is endothermic and therefore its transition state is product-like (here radical-like).[9] Attacks at C7/C15 affords a *p*-orbital well-aligned with the aromatic π-system, whereas that generated at C6/C14 would be nearly orthogonal and not delocalised. Hence, abstraction at the secondary benzylic site, rather than the tertiary one, is favoured. This view is supported by *ab initio* calculations[10] performed on compound **1** which revealed that the upper (α-face) C7/C15 C–H is the weakest of the three potential reactive C–H bonds based on charge distribution and bond lengths (Fig. 2). Once the benzylic radical has been generated, the V-shaped diquinoline molecular skeleton ensures that bromination will occur predominantly on the more exposed α-face to yield **2** or **4** as the final product.

These results reveal that solid-state NBS reaction can be a useful procedure for benzylic bromination that avoids the use of toxic CCl_4 or other solvents. Most importantly, the regio- and stereo-selectivity encountered in the solution phase reactions is retained when solvent is omitted. We are currently investigating the wider scope of this synthetic method.

Experimental

5bα,6,12bα,13-Tetrahydropentaleno[1,2-*b*:4,5-*b*′]diquinoline **1** (60.00 mg, 0.195 mmol) and NBS (120 mg, 0.674 mmol) were placed in a Retsch Mixer Mill (model MM200) grinding jar and the reaction mixture was ground at a frequency of 15 s^{-1}. The progress of the reaction was monitored in every one hour interval by using TLC and NMR. Until 4 hours of grinding, no reaction was observed. The reaction was started at the 5th hour and became complete at the 6th hour. The crude product was then mixed with a small volume of acetone and the soluble material decanted onto a flash chromatography column which was eluted by the same solvent. The solvent was evaporated under reduced pressure to obtain the pure compound **2** in 85% yield. Compound **4** was also synthesised using the same procedure. The IR, NMR, MS, EA and single crystal X-ray analysis of **1–4** were described elsewhere.[4a–c]

Acknowledgements

We gratefully acknowledge financial support from the Agency for Science, Technology and Research, Singapore.

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Solubility of unsaturated carboxylic acids in supercritical 1,1,1,2-tetrafluoroethane (HFC 134a) and a methodology for the separation of ternary mixtures†

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Received 17th August 2004, Accepted 24th December 2004
First published as an Advance Article on the web 1st February 2005
DOI: 10.1039/b412697a

The solubility of a variety of unsaturated carboxylic acids is determined in supercritical tetrafluoroethane (HFC 134a) at 90 °C using a capacitative method. The solubility is found to decrease in the order crotonic- > 6-methoxytetralone- > methylsuccinic- > α-acetamido-cinnamic- > itaconic acid. In all cases the solubility of the acid in HFC 134a was one to two orders of magnitude greater than that in CO_2 under comparable conditions; equivalent to *ca.* 20 fold reduction in the energy required to compress the gas needed to dissolve one mole of substrate. The solubility of the ternary system HFC 134a, methylsuccinic and itaconic acids was measured as a function of pressure and the dissolution selectivity for the two acids was characterised. The minimum number of stages required to separate methylsuccinic from itaconic acid is determined using equilateral triangle diagrams.

Introduction

Over the last few decades the solubilities of solids and liquids in sc fluids have been studied extensively,[1–5] and this information forms an important component in establishing the feasibility of any sc fluid for applications such as chromatography, extraction or chemical synthesis. Carbon dioxide is by far the most commonly employed sc solvent but solutes are limited to less-polar or highly volatile compounds. Branching and fluorination are known to enhance the solubility of solutes whilst unsaturation, acidic protons and phenyl substituents decrease solubility in sc CO_2.[6,7] The restriction to less-polar reagents and/or catalysts with non-aromatic ligands poses numerous potential problems and several strategies for increasing the solubility of compounds in non-polar fluids have been developed. These include the use of CO_2-philic tails, counter-ions and co-solvents. It is well known that the addition of polar co-solvents to sc CO_2 can greatly enhance the solubility of polar solutes[8–10] and this is generally attributed to the strong interaction between the co-solvent and solute. This explanation is based on results from spectroscopic studies[11,12] and molecular simulations.[13]

The low solubilities of very polar substrates in CO_2 can be avoided by using sc HFCs, although solubility data in sc HFCs are very limited. We previously determined the solubilities of several *p*-benzoic acids and *p*-phenols in HFC 32 and found that solubility was largely dependent on the identity of the functional group at the *para* position.[14] Stahl and Willing measured the solubilities of different alkaloids in sc CO_2, NO_2 and CHF_3[15] and found that the solubility of the alkaloids was higher in CHF_3 than in the other two solvents. Taylor and co-workers determined the solubility of sulfur containing solutes in sc CO_2, CHF_3 and HFC 134a.[16] Their results showed that the solutes had much higher solubilities in HFC 134a when compared to the other solvents. We have shown that HFC 134a is a relatively polar solvent, even in the sc domain, which may enhance the solubility of polar solutes,[17–19] and increased solubility in sc HFC 134a is thought to be a consequence of the higher dielectric constant and polarisability of this medium.

One of the major potential advantages of using HFCs is one of process intensification arising from higher solute solubilities. It has recently been shown that sc HFC 134a is effective as a reaction medium for a variety of reactions including asymmetric hydrogenation.[20] Hence the focus of this work is the effect of temperature, pressure and solute structure on the solubility of various potential substrates and their reduced products.

In the current work we use a dielectrometry technique[14] coupled with gravimetry to determine the solubility of a range of unsaturated carboxylic acids in HFC 134a. The Peng–Robinson equation of state (PR EOS) was used to model the solubility results for binary and ternary systems and the discussion extended to use the solubility information to model a counter-current extraction process for the separation of reagents and products.

Experimental

The solutes used for this study are outlined in Table 1. Two different methods of solubility determination were used in this work. The first was a dielectrometry technique, which has been described elsewhere.[14] Standardisation of the technique was carried out as previously using naphthalene and the data were found to agree with the published gravimetric data to ±1%. The second technique was a gravimetric one and used the solute trapped between two steel gauzes at the ends of a cylindrical pot (1 cm depth). Excess solute was placed into the

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† Electronic supplementary information (ESI) available: Tables of solubility data. See http://www.rsc.org/suppdata/gc/b4/b412697a/
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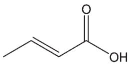
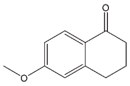
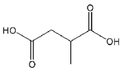
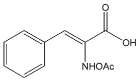
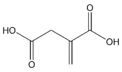
Table 1 The melting points and permanent dipole moments for the solutes used in this study

Solute	Structure	mp[29]/K	μ/D	Source
Crotonic acid		344	1.528	Fluka > 97%
6-Methoxy-1-tetralone		351	1.113	Arcos 99%
Methylsuccinic acid		388	1.076	Aldrich 99%
α-Acetamido-cinnamic acid		467	2.829	Aldrich 98%
Itaconic acid		439	3.327	Aldrich > 99%

stainless steel base and the weight was recorded. The gauze cover was screwed in place and the solute container was placed into the high-pressure cell. The cell was heated to the desired temperature and pressurised using the appropriate solvent. Once equilibration had been reached the cell was depressurised, the gauze cover was removed and the base was re-weighed. The separation experiments were carried out using the same equipment described for the gravimetric solubility determination above. A mixture of known composition of the compounds to be separated was placed into the solute container. The container was placed into the cell and the temperature and pressure conditions were set so as to preferentially solubilise one of the mixture components. Analysis of the base contents, post depressurisation, was carried out using NMR, GC-MS and GC.

Results and discussion

Solubility of solutes in supercritical HFC 134a

The experimentally calculated solubilities, obtained using the dielectrometry technique, for a variety of solutes in HFC 134a at 378 K and varying pressures are shown in Fig. 1. Some results using CO_2 as the solvent are shown for comparison in Fig. 2 and it can be seen that the solvating power of HFC 134a is much higher than that of CO_2 for these solutes.

For example, the solubility of crotonic acid in HFC 134a at 378 K and 50 bar is 2.62×10^{-1} mol L^{-1} whereas the solubility in CO_2, under the same conditions, is two orders of magnitude lower at 2.72×10^{-3} mol L^{-1}. This means that 3.8 L of HFC 134a and 367.9 L of CO_2 would be needed to dissolve one mole of crotonic acid at 50 bar and 378 K. The work needed to compress the required volumes of gas, in order to dissolve one mole of crotonic acid, are 341.9 kJ when using HFC 134a and 8×10^3 kJ when using CO_2 as the solvent. Hence the energy requirement for the process involving CO_2 is more than 20 times that using HFC 134a, although it has to be stressed that such a process would not normally be attempted using CO_2. This result does however show that HFCs are promising solvents for processes involving polar substrates in terms of energy requirements, economy and equipment design, since low reaction volumes are required.

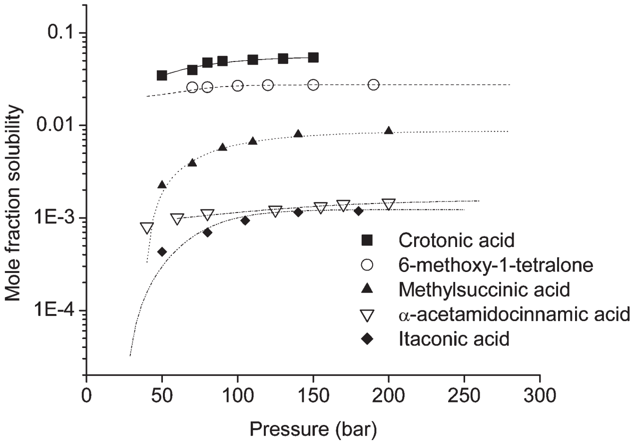


Fig. 1 Comparison of solubilities for various substrates in HFC 134a at 378 K and a variety of pressures.

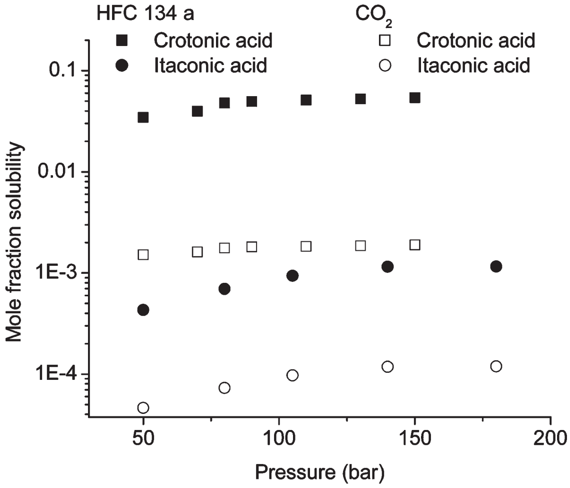


Fig. 2 Comparison of crotonic acid and itaconic acid solubilities in HFC 134a and CO_2 at 378 K and a variety of pressures.

It can be seen from Fig. 1 that the mole fraction solubility increases with increasing pressure for all of the solutes studied and it has been reported in a previous study[14] that solute solubility decreases with increasing polarity. Table 1 shows the permanent dipole moments and melting points (mp) for the solutes used in this study. The solute solubilities decrease in the order crotonic- > 6-methoxy-1-tetralone- > methylsuccinic- > α-acetamido-cinnamic- > itaconic acid, which does not follow the trend in polarity shown in Table 1. This is attributed to the fact that the experimental temperatures used in this work are higher than the melting points for crotonic acid and 6-methoxy-1-tetralone and, hence, these solutes are in the liquid state. Not only do these solutes have higher vapour pressures in the liquid state (at 378 K: 1.08×10^{-1} bar for crotonic acid and 2.97×10^{-4} bar for 6-methoxy-1-tetralone *cf.* 1.54 × 10^{-5} for methylsuccinic acid)[21] but also the energy of dissolution is lower due to the reduced solute–solute interactions in the liquid when compared to those in the solid state.

Generally, increasing the hydrostatic pressure increases the melting points of pure solids, but it is possible that the reverse is observed when solids are compressed in sc fluids and this effect is analogous to the freezing point depression of water when salt is added to it. As pressure is increased an increased amount of sc fluid dissolves in the liquid phase at the surface of the solid and, therefore, the temperature needed to freeze the solute to the solid phase decreases, since the liquid–solvent solution at the surface of the solid is not easily accommodated into the bulk solid lattice.

Since methylsuccinic acid has a melting point only 10 K higher than the experimental temperature, the phase behaviour of this solute was observed by placing an excess amount of solid in a windowed vessel, which was then subjected to the experimental conditions employed in this study. The solute remained solid under all conditions studied and this complements the explanation given above for the solubility trends of crotonic acid, 6-methoxy-1-tetralone and methylsuccinic acid.

Figs. 3 and 4 show several solubility isotherms for methylsuccinic acid and itaconic acid respectively. It can be seen that solubility increases with increasing temperature for both solutes studied. Most notably the solubility of methylsuccinic acid is considerably higher than that for itaconic acid. Since the former is the reduced product of the latter a synthetic process involving the reduction of the unsaturated acid in a sc fluid has the potential to incorporate product separation based on preferential solubility.

Kurnik and co-workers[22] reported that the solubility of solid solutes in sc CO_2 could be correlated using the PR EOS and this PR model is used in this work to correlate the solubility of a number of solutes in HFC 134a using solute physical and chemical properties. The pure solute data used in the PR EOS model are summarised in Table 2. Figs. 1, 3 and 4 compare the experimental and theoretical solubilities for the solutes studied in this work and the results have a maximum root mean square correlation error of ±0.0014. It can be seen from these plots that there is good agreement between the experimental and theoretical data for the temperature and pressure ranges investigated. This is an indication that the PR EOS can be used to predict solute solubilities in sc HFC 134a.

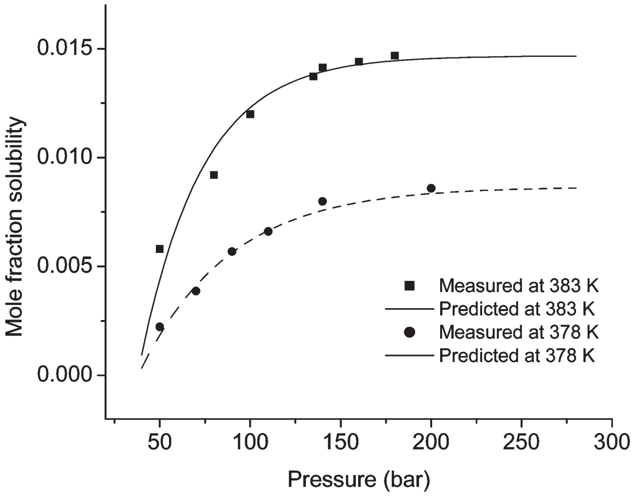


Fig. 3 Comparison of experimental and theoretical solubility data for methylsuccinic acid in HFC 134a along two different isotherms and a variety of pressures.

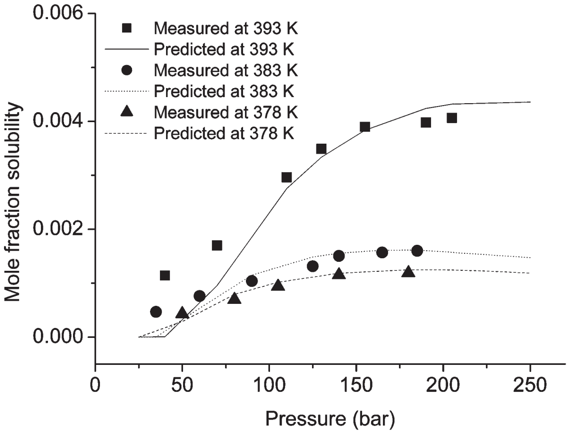


Fig. 4 Comparison of experimental and theoretical solubility data for itaconic acid in HFC 134a along three different isotherms and a variety of pressures.

Table 2 Pure solute data used to model solubilities using the PR EOS

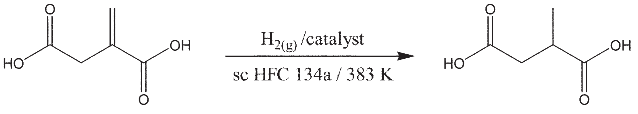
Solute	v/m^3 mol^{-1a}	T_c/K	P/bar	ω^d	k_{ij}^e
Crotonic acid	6.55 × 10^{-5}	647.5^b	47.0^b	0.572^b	−1.35
6-Methoxy-1-tetralone	1.13 × 10^{-4}	831.6^c	30.9^c	0.589^c	−0.98
Methylsuccinic acid	9.04 × 10^{-5}	817.2^c	41.1^c	1.033^c	−1.43
α-Acetamido-cinnamic acid	1.42 × 10^{-4}	963.2^c	28.3^c	1.015^c	−0.88
Itaconic acid	8.56 × 10^{-5}	821.0^b	42.4^b	0.925^b	−0.36

[a] Solute molar volume. Estimated using Spartan Pro.[31] [b] Published data.[32] [c] Estimated using Cranium.[21] [d] −log(reduced pressure) − 1. [e] Binary interaction parameter. Obtained from experimental data.

Designing a separation process

It has previously been shown[20] that alkenes can be effectively reduced in sc HFC 134a with high yields (>90%) and high enantiomeric excess (>80%) (Scheme 1). It is, therefore, important to establish that a sc methodology can be developed to separate the alkene substrate from the reduced product. In this section we use equilateral triangle diagrams to calculate the minimum number of stages required to separate the reagents and products in Scheme 1. This will clearly need experimental justification, but it is important to show the feasibility of such a process.

The separation strategy employed is based upon the difference in solubilities between the itaconic acid (1) and the methylsuccinic acid (2). For the purpose of this initial



Scheme 1 The hydrogenation of itaconic acid in sc HFC 134a at 383 K and various pressures.

separation study only the solubility of the reagent and product will be considered and the catalyst will be ignored because of its low concentration in the reaction mixture. To a first approximation we will determine the effect that each solute has on the solubility of the other. However, the solubility studies here employed an equimolar mixture of the two compounds in excess, so that a saturated solution was obtained giving an indication of the solvating ability and solvating preference of HFC 134a for each solute in this ternary system.

It is important to realise that the solubilities of solutes can be greatly affected by the presence of species other than the solvent. This effect is shown in Fig. 5 where the solubilities of itaconic acid and methylsuccinic acid in HFC 134a are given for both binary and ternary systems at 383 K and varying pressures. The difference in solubilities between the two compounds in the ternary system is much less than the difference between those for the binary systems, and this will have an influence on the selection of separation conditions. Therefore, separation strategies based on solubility data should employ results obtained for systems in which all species are present in the mixture to be fractionated.

It can be seen that the solubility of itaconic acid in the ternary system is enhanced (compared to the solubility in the binary system), whereas that of methylsuccinic acid is decreased. An appreciation of the solubility enhancement (***SE***) in ternary systems can be gained by using

$$SE = \frac{y_t - y_b}{y_b} \times 100\% \qquad (1)$$

where $\boldsymbol{y}_\mathbf{t}$ and $\boldsymbol{y}_\mathbf{b}$ are the mole fractions of the solute in solution for the ternary and binary systems respectively. At a given temperature there will be several values of ***SE*** for a given component and, therefore, average values will be used to quantify the solubility enhancement in this work.

The solubility enhancement for itaconic acid is calculated to be 109.3% and that for methylsuccinic acid is calculated to be −53.7%. The negative ***SE*** value obtained for methylsuccinic acid denotes the observed decrease in solubility in the ternary system relative to the binary system (solubility diminution). Solubility diminution has been observed previously[23] but published data for such systems is scarce and, to date, no explanations for this phenomenon have been proposed.

Positive solubility enhancement is more easily explained. It is well known that the addition of co-solvents (or entrainers) to sc fluid systems can lead to increased solubility for a given solute. Similarly, the presence of other components in mixed solute systems can enhance the solubility of one or more of the species due to solute–solute interactions. This is particularly applicable if the solutes contain potential hydrogen bonding sites,[24] which is the case with the solutes under investigation in this work and this explains the positive enhancement in the solubility of itaconic acid.

The applicability of the PR EOS to model solubility in the ternary system under investigation was tested and the results are shown in Fig. 5. Quadratic mixing rules were used in conjunction with the PR EOS and the results had a maximum root mean square correlation error of ±0.0003. Although the PR EOS has previously been used to model ternary systems in CO_2,[25] this is the first time the model has been employed to model solubility in a ternary HFC 134a system comprising two solid components. It can be seen that this model adequately describes the solubilities of the solutes in this system and the PR EOS was, therefore, used to perform the required calculations in order to develop the separation process. All phase calculations were performed using the Phase Equilibria computer package[26] and the data required for the separation model was exported from the program. Fig. 6 shows the saturation curves of the system under investigation and the figure contains an inset to show the vapour saturation curve more clearly (some example tie lines are shown).

The extraction pressure is taken to be the pressure at which the selectivity (or separation factor) of the sc fluid is greatest. The selectivity is defined as the ratio of the solubilities of the more to the less soluble solutes respectively, and those based on the ternary system solubility data are shown in Fig. 7 as a function of pressure. It can be seen that selectivity decreases with increasing pressure for this system and that the greatest selectivity is observed at 55 bar. The percentage conversion in the reactor will give a product stream, which represents the feed, *F*, which must be dealt with in the SFE process.

The model described here for the separation process will employ a counter-current separating column with a multistage separation module in which the feed (HFC 134a, itaconic acid

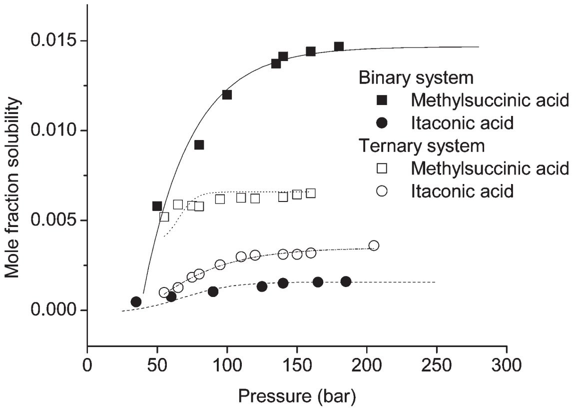


Fig. 5 Comparison of binary and ternary system solubility data for itaconic acid and methylsuccinic acid in HFC 134a at 383 K.

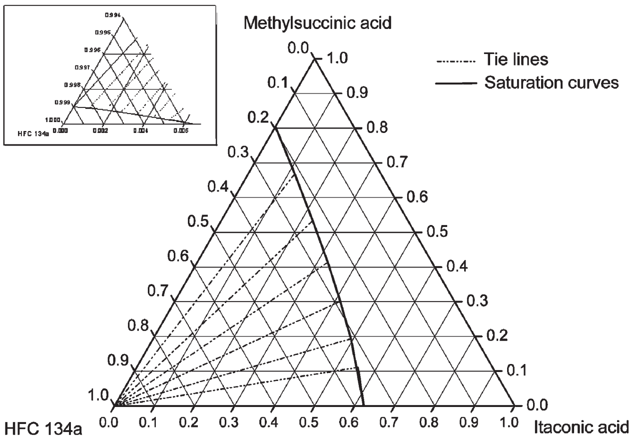


Fig. 6 The saturation curves for the ternary system at 55 bar and 383 K. The inset shows the vapour saturation curve more clearly.

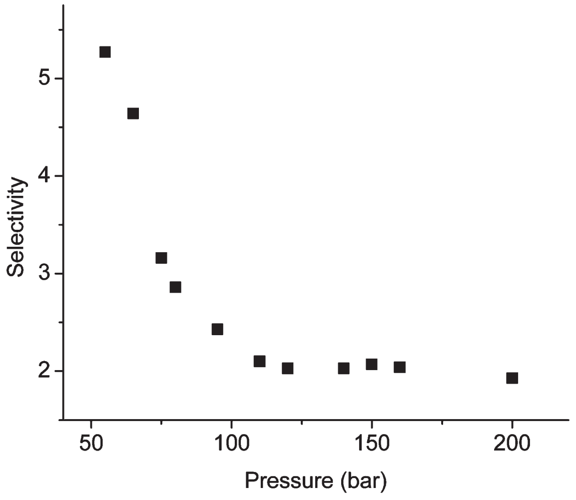


Fig. 7 Selectivity as a function of pressure for itaconic acid and methylsuccinic acid in HFC 134a at 383 K.

and methylsuccinic acid) enters the top of the column, and the raffinate (HFC 134a and itaconic acid), *R*, leaves the bottom (stage number *N*). The raffinate is defined as the portion of the original feed left over once the desired component (methylsuccinic acid in this case) has been extracted with solvent, and the raffinate phase can be recycled to the reaction vessel and the starting material reused.

The solvent stream, *S*, of HFC 134a enters the bottom of the column and flows counter-current to the descending raffinate phase, thus extracting the desired component. The extract phase (HFC 134a and methylsuccinic acid), *E*, exits the top of the column.

The remainder of this discussion will involve the determination of the required number of stages in the column to achieve the desired fractionation of components. Theoretical reaction conversion values of 50% and 95% are dealt with and the SFE process for intermediate conversions will require an intermediate number of stages in the separating column. The following assumptions are necessary in order to simplify the design process:[27]

1. The two flows, *F* and *R*, entering each stage are merged into a single flow.

2. The pressure and temperature for the SFE process are exerted externally and are the same for every stage. Energy balances are considered negligible and are neglected.

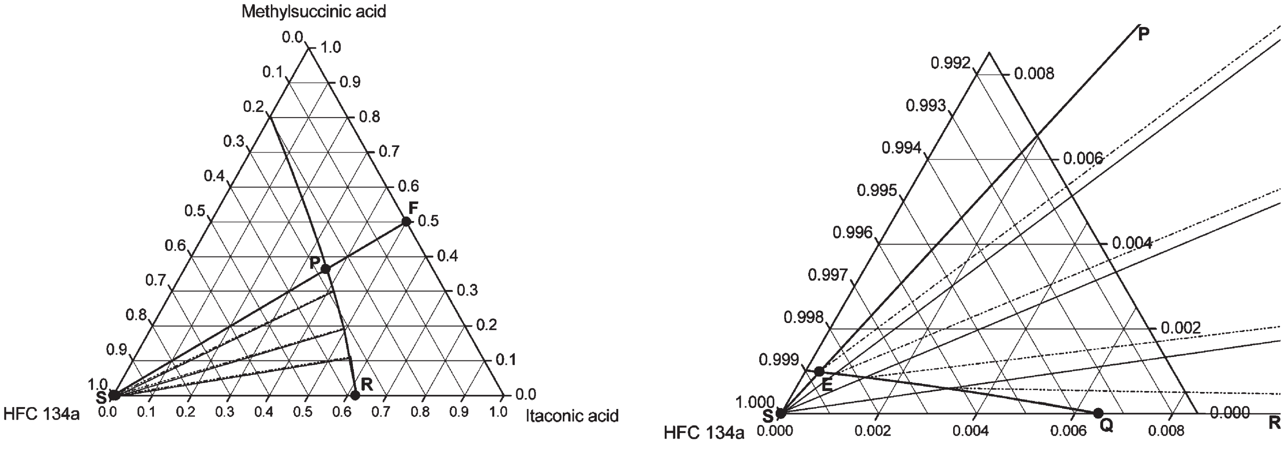
3. The extract and raffinate phases leaving each stage are in equilibrium and perfectly homogeneous.

For a counter-current separating column the minimum number of theoretical stages required can be obtained by the construction of equilateral triangle diagrams, the method of which is described in detail elsewhere.[28,29] Figs. 8 and 9 show the equilateral triangle diagrams for the processes involving a 50% and 95% conversion respectively.

To simplify construction of the diagrams further, the minimum number of stages required to achieve separation is regarded as the point at which the methylsuccinic acid concentration in the raffinate becomes zero, which dictates the position of point *R*. This means that the construction lines run from point *S* in the diagram and reach their maximum value.

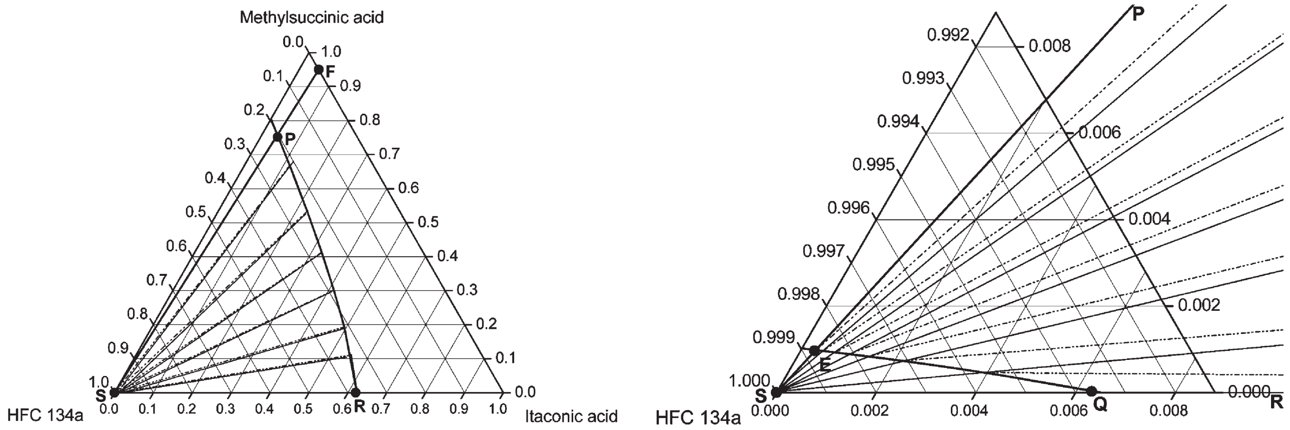
The lines *F*–*S* and *R*–*S* represent the upper and lower construction lines respectively and any other line that lies between *F*–*S* and *R*–*S* represents an intermediate construction line. The couples *R*–*Q* and *P*–*E* represent the start of the operating line and the end of the operating line respectively. The number of stepwise construction and tie lines in the diagram gives the number of stages required for separation. This corresponds to four stages for the 50% methylsuccinic acid feed and seven steps for the 95% methylsuccinic acid feed. Estimations from the triangle diagrams suggest that >99% of the methylsuccinic acid is extracted from each system, although a true representation of the SFE results would be obtained using computational simulations incorporating phase flow rates, which is beyond the scope of this study.

The discussion here is by no means exhaustive and the theoretical aspects employed during the design of the separation process are based on theoretical PR EOS calculations



(a) (b)

Fig. 8 (a) The equilateral triangle diagram used to determine the minimum number of stages for counter-current separation of a 50 : 50 reagent to product feed. (b) An enlargement showing the vapour saturation curve and the extract phase.



(a) (b)

Fig. 9 (a) The equilateral triangle diagram used to determine the minimum number of stages for counter-current separation of a 5 : 95 reagent to product feed. (b) An enlargement showing the vapour saturation curve and the extract phase.

involving initial estimate data. The models have been made as simple as possible to serve as an example of how solubility data can be used in process design. A more detailed and realistic study should involve an experimental investigation of system phase behaviour of the components present in the mixture.

These initial models do, however, suggest that it is possible to carry out sc fluid reactions in a system incorporating an in-line SFE process, which is beneficial in terms of economic and engineering strategies. It is shown that HFC 134a can be used not only as the reaction medium but also the extracting solvent and that efficient separation of reagents and products can be achieved, which greatly enhances the commercial applicability of this technology.

Conclusion

The solubilities of a range of polar solutes in HFC 134a have been investigated. It was shown that solubility increases with increasing pressure for all solutes studied and also with increasing temperature for itaconic acid and methylsuccinic acid. It has been reported previously that solubility decreases with increasing solute polarity.[14] This general trend was also observed in this work although it was shown that these trends can be changed if the experimental temperature exceeds the melting point temperature of the solute. The study also extends current data pertaining to the solvating power of HFCs, since publications to date are very limited.

It has been demonstrated that polar solutes have much higher solubilities in HFC 134a than in CO_2 and that the energy requirements needed to obtain similar solubilities in pure CO_2 are over an order of magnitude higher than those for the HFC 134a system. The higher energy requirement associated with CO_2 greatly reduces the attractiveness of this solvent for processes involving polar reagents, analytes or substrates and HFCs have been shown to be viable alternatives for such processes. Clearly there are other environmental issues concerned with the manufacture of HFCs and this has to be contrasted with their lifetime in the environment compared with CO_2. However, this is a complex matter and is explained in greater detail elsewhere.[20]

The higher solubilities in HFC 134a are due to the higher dielectric constant of this medium, which changes considerably with increasing pressure, especially around the critical point. This suggests that varying degrees of enantioselectivity can be achieved during asymmetric synthesis in this solvent.

The data for the binary system was successfully modelled using the Peng–Robinson equation of state and for the first time this work applied the model to successfully correlate the solubilities of a ternary HFC 134a system comprising two solid solutes. This shows that the PR EOS could be a useful tool for predicting solute solubilities in HFC 134a and predictions of this sort may prove to be convenient alternatives to experimental data during initial process design.

The importance of solubility data was demonstrated by modelling an ideal supercritical fluid extraction process, for the separation of reagents and products, using a counter-current separating column.

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A new method for the synthesis of triaryl phosphates

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Received 12th November 2004, Accepted 17th February 2005
First published as an Advance Article on the web 25th February 2005
DOI: 10.1039/b417264g

Triaryl phosphates were obtained by a new, efficient and environmentally friendly method, the vapor–liquid condensation of phosphorus oxychloride with hydroxyaryl compounds. Phosphorus oxychloride was heated and carried by a stream of nitrogen into a solution containing 20% aqueous sodium hydroxide and hydroxyaryl compound. Triaryl phosphates obtained as the solid products were separated by filtration, purified, dried under vacuum and characterized by IR, ^{1}H-NMR, ^{31}P-NMR and HPLC.

Introduction

Triaryl phosphates, namely triphenyl phosphate, tricresyl phosphate, *etc*. are used in different industrial applications such as plasticizers for cellulose acetate, polyvinylchloride and vinyl polymers, fireproofing agents for phenolic resins, polyurethanes, unsaturated polyesters, hydraulic fluids and gas-turbine lubricants.[1] Recent reports implicate these compounds in photosensitive materials[2] and as endocrine and reproductive toxicants in rodents.[3]

Triaryl phosphates have been synthesized by several methods. They are conventionally synthesized on an industrial scale by reacting hydroxyaryl compounds with phosphorus pentachloride,[4] phosphoric acid[5] or phosphorus oxychloride. The reaction with phosphorus oxychloride is carried out in solvents and with catalysts, such Mg, Ca, Al or $MgCl_2$, $CaCl_2$ or $AlCl_3$, *etc*.[6] Bhagat and Mathur[7] have phosphorylated the substituted phenols with $POCl_3$, following the multistage heating procedure required for successive displacement of the chlorine atoms of $POCl_3$. One disadvantage of this process lies in the high temperatures at which the reactions have to be carried out and which are necessary for removal of the hydrogen chloride gas formed. The high temperature promotes the formation of dark-brown, tarry contaminants. These problems can be circumvented by the use of phase transfer synthesis of phosphorus oxyhalides, phosphorus pentahalides or phosphoric acid monoester halides, phosphoric acid diester halides with hydroxyaryl compounds, in the presence of catalysts, aqueous alkaline metal hydroxide solutions and organic water-immiscible solvents.[8–11] The advantages of this method are: esters can be purified by simple crystallization, shorter reaction times, better yields, *etc*. An efficient and simple method for triaryl phosphate synthesis was the reaction of phosphorus oxychloride with insoluble polymer-supported phenoxide ion reagents.[12] Another method for triaryl phosphate synthesis is a "one-pot" synthesis through the reaction of sodium phenoxides with phosphorus oxychloride.[13,14]

In this paper we report the synthesis of triaryl phosphates by a new, simple, efficient and environmentally friendly method, the vapor–liquid interfacial condensation of phosphorus oxychloride with various phenols (phenol, *p*-cresol, *p*-chlorophenol and *p*-nitrophenol). This system utilizes pairs of highly reactive reagents with one of the reagents ($POCl_3$) in the vapor state and the other (*i.e.* phenol) in solution. The contact of the reagents in the vapor–liquid reaction is readily performed by bubbling the vapor (gaseous) reagent through an aqueous solution of the other reagent. The use of an organic solvent is not required.

Experimental

Materials

Phenol, *p*-cresol, *p*-chlorophenol and *p*-nitrophenol were supplied by Aldrich and were distilled prior to use.

Instruments

The IR spectra were recorded on a SPECORD M80 spectrophotometer (film) and the ^{1}H-NMR and ^{31}P-NMR spectra were recorded on a Bruker Avance DRX 400 at 400 MHz (85% H_3PO_4 was used as external standard for ^{31}P and TMS as internal standard for ^{1}H). ABL&E JASCO HPLC was used to establish the purity of the products on a C_{18} column with UV detector (MD-1510).

General procedure

For the liquid–vapor interfacial condensation we have used the experimental apparatus presented in Fig. 1. In round-bottom

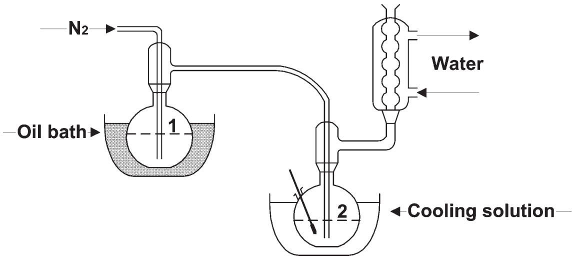
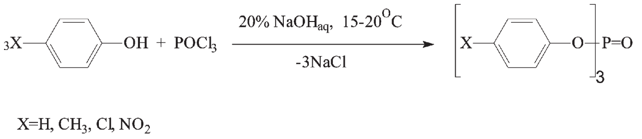


Fig. 1 Experimental apparatus for the vapor–liquid synthesis of triaryl phosphates.



Scheme 1 The synthesis of triaryl phosphates.

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Table 1 Triaryl phosphates obtained by vapor–liquid technique[a]

		Melting point/°C				
Triaryl phosphates	Yield (%)	Found	Reported[15]	IR/cm^{-1}	^{1}H-NMR[b,c] (ppm)	^{31}P-NMR[d] (ppm)
Triphenyl phosphate	95	49	49–51	1302 (P=O) 1195, 955 (P–O–C)	7.2 (1H,m)	−19.6
Tris(*p*-cresyl) phosphate	90	77	77.5–78.7	1305 (P=O) 1180, 1145, 970 (P–O–C)	7.1 (4H,m); 2.4 (3H,s)	−19.0
Tris(*p*-chlorophenyl) phosphate	92	112	112–113	1300(P=O) 1190, 1090, 980 (P–O–C)	7.0 (1H,m) 7.3 (1H,m)	−19.9
Tris(*p*-nitrophenyl) phosphate	90	156	155–156	1300 (P=O) 1185, 1150, 960 (P–O–C)	7.4 (1H,d) 8.4 (1H,d)	−21.8

[a] Reaction conditions: reaction temperature 15–20 °C (reaction temperature in flask 1 = 70 °C); molar ratio $POCl_3$: hydroxyaryl compounds = 4 : 1; reaction time 40 min. [b] In $CDCl_3$ with TMS as internal standard. [c] s = singlet; d = doublet; m = multiplet. [d] In $CDCl_3$ with 85% H_3PO_4 as external standard.

flask 1, which was immersed in an oil bath, the appropriate phosphorus oxychloride was heated (70 °C) and carried by a stream of nitrogen into flask 2, containing an aqueous 20% sodium hydroxide solution and the hydroxyaryl compound. The nitrogen stream acts as carrier gas for the phosphorus oxychloride, as a reaction mixture protector from atmospheric oxygen and for agitation of the reaction mixture. The reaction rate can be controlled by the nitrogen flow rate. The entire quantity of phosphorus oxychloride is transported with nitrogen from round-bottom flask 1 to flask 2. In order to prevent the possibility of condensation of the vapors on apparatus walls, the vapor mixture is overheated or is diluted so that the partial pressure of the vapor reagent in the gas mixture is lower than its saturation vapor pressure.

The carrier gas flow, which produced bubbles in the formed product that expanded and burst at the top of the reaction flask, was continued 15 min after the entire quantity of phosphorus oxychloride was trained. The solid product obtained was separated by filtration and washed with aqueous 2% sodium hydroxide solution (3 × 250 ml), water (until the wash solution had a neutral pH) and dried under vacuum.

Results and discussion

Triaryl (phenyl, *p*-cresyl, *p*-chlorophenyl, *p*-nitrophenyl) phosphates were synthesized by reacting phosphorus oxychloride (vapor) with sodium salts of the corresponding hydroxyaryl compounds in a vapor–liquid system: (Scheme 1)

The crude product was crystallized from petroleum ether (60–80 °C)–ethanol and its purity was checked by HPLC.

The product obtained by the vapor–liquid technique contains strongly adsorbed water which should be removed prior to further ester characterization and processing. This can be achieved by means of effective drying, for example, under vacuum.

The most appropriate conditions for the synthesis of triaryl phosphates by this technique are as follows:

- reaction temperature about 20 °C; the reaction is exothermic and the reaction temperature is controlled by a cooling solution.
- molar ratio $POCl_3$: hydroxyaryl compounds = 4 : 1.
- the duration of an experiment may vary but should not be so great as to effect a considerable decrease in the monomer concentration of the liquid phase.

The yields, the melting points for the obtained triaryl phosphates and the data for IR, ^{1}H-NMR and ^{31}P-NMR are presented in Table 1. Near quantitative yields were obtained by this technique.

Conclusion

To summarize, we have described a new, simple, efficient and environmentally friendly method for the synthesis of triaryl phosphates involving a vapor–liquid condensation, which differs from liquid–liquid phase-transfer synthesis in its simplicity. In a vapor–liquid system, only ionic impurities (*i.e.*, NaCl) need to be washed from the crude product, while in a liquid–liquid system the separation procedure of an organic solvent from the product can be rather involved (steam distillation, *etc.*). Solvent recovery is not required in the synthesis of triaryl phosphates by the vapor–liquid technique. This method also permits the use of a wide range of phosphorus reagents in the reaction and can be generalized to other acylchlorides. Studies concerning these compounds are in progress.

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Telomerization of butadiene with pentoses in water: selective etherifications

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Received 2nd December 2004, Accepted 28th February 2005
First published as an Advance Article on the web 7th March 2005
DOI: 10.1039/b418236g

Conditions have been developed to achieve the palladium catalysed telomerization of butadiene with L-arabinose and D-xylose in aqueous medium. The success of the reaction requires the presence of a tertiary amine as promoter with a catalytic system based on Pd–TPPTS. The etherification first occurs on the anomeric hydroxyl and, depending on the amine used, a second etherification leads to formation of the diether.

Since the discovery of the butadiene palladium-catalysed telomerization reaction in 1967,[1] the constant effort devoted to its development has been connected to the potential applications of the telomers, which depend on the telogens employed,[2] and is illustrated by the number of patents.[3,4] Selectivity in telomerization reactions remains a challenge since various parameters influence the reaction course and even interact with each other. Some detailed studies of the butadiene telomerization mechanism have given a deeper insight into the different steps of the catalytic cycle,[5–7] and conditions have been determined in order to achieve a selective grafting of the linear (*versus* branched, designated as l/b ratio) octadienyl chain when methanol[7] or ammonia[8] are the nucleophiles.

When a polynucleophile is employed, the selectivity involves not only the l/b ratio, but also the number of reacting nucleophilic functions. The ratios of mono- *versus* disubstitution by the octadienyl chain have been studied starting from bifunctional active hydrogen compounds. A high selectivity to monosubstituted linear telomers has been achieved with ethylene glycol[9] and ammonia in biphasic systems[8,10] or from ethylene glycol and aminoalcohols by using polymer-bound palladium(0) complexes as the catalysts.[11] Aminoalcohols also gave the selective octadienylation of the amine function under most of the homogeneous conditions employed.[12]

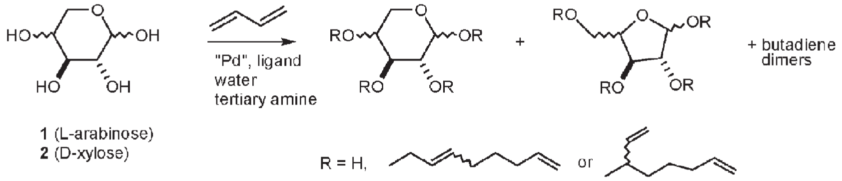
The use of raw sugars as telogens is of great interest due to the direct transformation of these renewable materials into biodegradable non ionic surfactants.[13] Telomerization reactions have thus been carried out with glucose or its derivatives,[14] sucrose[15–17] and even with polysaccharides such as starch.[18] However with these nucleophiles, the situation is much more complicated, due to the existence of tautomers adding to the multiplication of reactive sites. Nevertheless, conditions have been described to carry out the selective monoetherification of sucrose in isopropanol–water mixtures[16,17] and we have previously disclosed the selective grafting of one octadienyl chain on the anomeric hydroxyl of L-arabinose and D-xylose in DMF.[19] In order to develop greener methodologies, we have continued our studies in aqueous media and we wish to report here conditions which give the selective etherification of the above pentoses with one or two octadienyl chains. We also describe our attempts in recycling the Pd-catalyst.

Results and discussion

Reaction analysis

Preliminary experiments were carried out in a 50 mL autoclave using excess butadiene and a concentrated aqueous solution of L-arabinose or D-xylose (1 g per 0.5 mL H_2O) in order to minimise octadienol formation. The catalytic system was based on $Pd(acac)_2$ in conjunction with a water-soluble phosphine as ligand, the sodium salt of tris-(3-sulfonatophenyl) phosphine[20,21] (TPPTS). After reaction, the solvent and the butadiene dimers (1,3,7-octatriene and 4-vinylcyclohexene) were removed by distillation and the residue was peracetylated before analysis by GC-MS. The sugar derived products (Scheme 1) were identified on the basis of their mass spectra as groups of mono- or poly-ethers, a similar distribution being observed starting from L-arabinose or D-xylose. The structures of the main monooctadienylpentosides were identical to those previously attributed to the butadiene telomerization carried out in DMF.[4,19] As revealed by GC-MS, structure assignment was more complicated for the dioctadienyl pentosides. Indeed, the butadiene telomerization with L-arabinose led to a complex mixture due to its multiple reactive sites in its pyranose and furanose forms, associated with the possible formation of chain isomers. The mixture issued from the reaction with D-xylose was slightly easier to analyse since the telomerization takes place mainly from the pyranose form, thus diminishing the number of possible isomers.

The major diethers from D-xylose consisted of three compounds in similar quantities (about 25% of **2β**, 25% of **3β** and 30% of **4β** (Fig. 1) as well as unidentified isomers in minute amounts. These compounds were identified by comparison of their NMR spectra with those of the peracetylated starting sugars[22] and monooctadienylpentosides.[4,19] As previously observed for the telomerization of butadiene with pentoses in DMF,[19] the first etherification mainly occured at the anomeric hydroxyl, probably due to its higher acidity compared to that of the other groups.[23] The second etherification took place on the other hydroxyls of comparable acidity with similar rates leading to a similar distribution for **2**, **3** and **4**. The identified xylose derivatives were all in a pyranose form with substituents in an equatorial position and with an (*E*)-configuration of the double bond for the hydrophobic chains.



Scheme 1 Telomerization reaction of butadiene with L-arabinose and D-xylose.

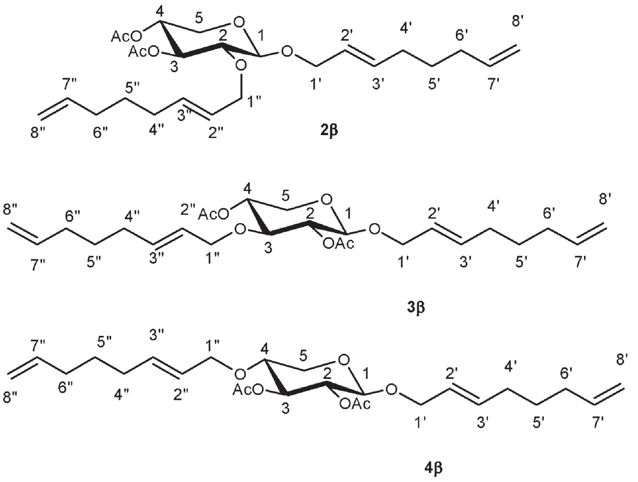


Fig. 1 Structures of the acetylated dioctadienylxylosides resulting from the telomerization of butadiene with D-xylose in water.

Effect of a base as additive

As previously observed,[15–18,20] the presence of a base was required for telomerization carried out in an aqueous medium, since the sugar was unchanged after 45 min at 80 °C without any base (Table 1, entry 1) or with a low amount of NaOH (entry 2). Some conversion (28%, entry 3) took place by increasing the NaOH concentration. However, under these basic conditions, the GC-MS analysis indicated some isomerization of the arabinose since more than four isomers were detected for the recovered sugar. To avoid such an isomerization[24] the use of an organic base was examined. With one equivalent of NEt_3 the conversion reached 96% in 45 min (entry 4) and 100% in 90 min (entry 5). However all of the hydroxyl group were reactive since the triethers formed in low amounts in 45 min became the main adducts in 90 min, with tetraethers also being present. Decreasing the NEt_3/L-arabinose ratio to 0.5 did not greatly modify the results (entry 7), while a further decrease was strongly detrimental to the conversion (entry 8). These observations urged us to examine other amines. Diisopropylethylamine and *N*-methylpyrrolidine led to moderate conversions but with good selectivities in monoethers (entries 9–11) while dimethyldodecylamine allowed a good conversion leading to diethers as the main products (entries 12–14). D-Xylose exhibited a behaviour similar to that of L-arabinose under selected conditions (entries 6, 10 and 14 for xylose, compared to 4, 9 and 13 respectively for arabinose).

The presence of the tertiary amine is crucial, since not only the conversion values but also the selectivities are influenced. The base can react in multiple ways: by increasing the sugar nucleophilicity,[25,26] by facilitating the reduction step of the Pd(II) precatalyst to an active Pd(0) complex,[26,27] by establishing a ligation with the metal for its activation[28] or by participating in the catalytic cycle.[29] With NEt_3 and dimethyldodecylamine high conversions were observed, without selectivity in the former case and with major diether formation in the latter (entries 4–7 compared to 12–14). The second etherification of the firstly formed pentoside could be due to the amphiphilic character of the ammonium salt issued from $Me_2NC_{12}H_{25}$[30] allowing an enhanced reactivity of this pentoside in the aqueous medium. A fair conversion leading mainly to monoethers was observed with the more sterically hindered $EtN(i\text{-}Pr)_2$ or *N*-Me-pyrrolidine, (entries 9–11), while the corresponding ammonium salts did not exhibit amphiphilic properties. The implication of the amine as a palladium ligand could explain such selectivity modifications. Thus, by a simple

Table 1 Butadiene telomerization with pentoses: influence of the base[a]

Entry	Sugar	Base (equiv./sugar)	Time/min	Conv.[b] (%)	Ether selectivity[b] mono : di : tri : tetra (%)
1	**1**	0	45	0	0
2	**1**	NaOH (0.75×10^{-2})	45	0	0
3	**1**	NaOH (0.75×10^{-1})	45	28[c]	50 : 50 : 0 : 0
4	**1**	NEt_3 (1)	45	96	35 : 53 : 12 : 0
5	**1**	NEt_3 (1)	90	100	0 : 25 : 50 : 25
6	**2**	NEt_3 (1)	45	69	35 : 55 : 10 : 0
7	**1**	NEt_3 (0.5)	45	80	34 : 60 : 6 : 0
8	**1**	NEt_3 (0.16)	45	4	100 : 0 : 0 : 0
9	**1**	$EtN(iPr)_2$ (1)	45	63	79 : 21 : 0 : 0
10	**2**	$EtN(iPr)_2$ (1)	45	67	70 : 30 : 0 : 0
11	**1**	*N*-Me-pyrrolidine (1)	45	63	79 : 21 : 0 : 0
12	**1**	$Me_2NC_{12}H_{25}$ (0.5)	45	67	13 : 52 : 29 : 6
13	**1**	$Me_2NC_{12}H_{25}$ (1)	45	99	4 : 57 : 37 : 2
14	**2**	$Me_2NC_{12}H_{25}$ (1)	45	83	21 : 66 : 13 : 0

[a] Conditions: $Pd(acac)_2$ 4.4×10^{-5} mol; molar ratios: sugar : butadiene : Pd : TPPTS = 150 : 2250 : 1 : 3; 80 °C; 1 g of sugar in 0.5 mL H_2O. [b] GC evaluation. [c] Recovered sugar exhibits more than the four starting tautomer forms as indicated by GC-MS.

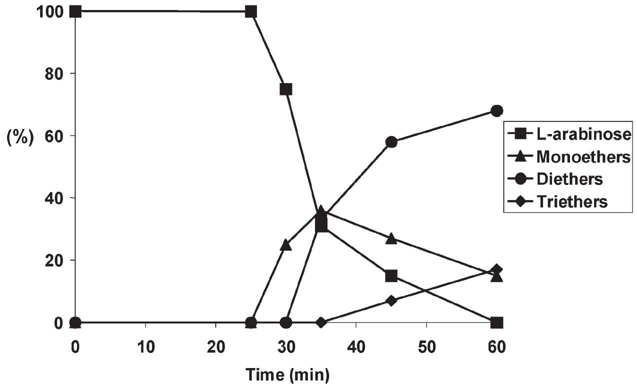


Fig. 2 Effect of reaction time on sugar transformation (conditions: entry 13, Table 1).

change of the tertiary amine structure, the reaction can be directed to the selective grafting of one or two octadienyl chains on the pentose. The preparation of molecules with different surfactant properties are among the many potential applications of this reaction.

Since phosphine as a *ligand* also plays an important role in telomerization reactions,[2] we examined the effect of the amount of TPPTS using the conditions of Table 1, Run 13: a better conversion of L-arabinose (99%) was observed for 3 equiv. TPPTS per palladium. A slight decrease (to 90%) was observed when the relative amount of phosphine increased to 4 equiv. The conversion dropped to less than 5% when the phosphine amount was reduced to 1 or 2 equivalents per palladium.

Development of the reaction over time

By examining the sugar transformation over time in the presence of dimethyldodecylamine, we found that no conversion occurred during the first 25 min (Fig. 2) with a fast reaction thereafter. Obviously the L-arabinose first led to the arabinoside which itself reacted in less than ten minutes. After 35 min, the sugar and its monoethers disappeared with comparable rates and the diethers became the major compounds, even at whole sugar conversion (60 min). The induction period required is probably related to the formation of an active catalyst. It has been reported that the reduction step of Pd(OAc)$_2$-(TPPTS)$_2$ is very fast in aqueous media, leading however to a palladium(0) complex considerably less reactive than the corresponding Pd(0) associated with PPh$_3$ in oxidative addition to phenyl iodide in the Heck reaction carried out in organic media.[31] If a similar spontaneous reduction for Pd(acac)$_2$-(TPPTS)$_2$–H$_2$O is assumed, the metal reduction would not be a determining step, contrary to the oxidative dimerization of butadiene involved in the catalytic cycle of the telomerization reaction.[5–7] The proposed amine surfactant effect could explain the fast reaction of the monoethers. Under these conditions the diethers, which are crowded and completely water insoluble, are separated from the aqueous phase and thus less prompt to react.

Effect of added cosolvent in biphasic media

Our further studies dealt with the use of different biphasic media, with the goal of increasing the selectivities. It has been reported that working in aqueous–organic biphasic systems not only allows enhanced selectivities, thanks to the extraction of the primary formed telomers,[8–10] but also offers the possibility of recovering and recycling the aqueous phase containing the catalyst.[8–10,32] Obviously, the solubility of sugar derivatives in water decreased with the number of fixed C-8 chains, diethers being *quasi* insoluble. Experiments under the above conditions and with Me$_2$NC$_{12}$H$_{25}$ afforded the results summarised in Table 2. A biphasic medium consisting of water–butadiene, has been reported giving high selectivity towards the linear monosubstituted compound with ammonia or glycols as telogen.[8–10] In our case, the use of 6 instead of 15 equiv. of butadiene per sugar was sufficient to observe good conversion and diether selectivity (entries 1 and 2), but a further decrease of the butadiene amount corresponded to a large decrease of the sugar conversion (entry 3). We also tested methylisobutylketone and 2-methoxyethanol (or methylcellosolve) as cosolvents; the former was an efficient solvent for the extraction of monooctadienyl sucrose[16] and the second a highly polar solvent having surfactant properties and a considerable homogenising ability.[33] With these two solvents diether selectivity improved slightly at butadiene/sugar ratios of 15 and 6 (entries 4, 5, 7 and 8), while for a ratio of 3 (entries 6 and 9) poor selectivities were observed in spite of a conversion increase compared to entry 3, Table 2 (without added cosolvent). The telomerization reaction was less efficient with methoxyethanol (entry 10, Table 2), as compared to the

Table 2 Influence of a cosolvent on the selectivity[a]

Entry	Cosolvent except butadiene	Molar ratio butadiene/sugar	Amine	Conv.[b] (%)	Ether selectivity[b] mono : di : tri (%)
1	—	15	Me$_2$NC$_{12}$H$_{25}$	99	4 : 57 : 37[c]
2	—	6	Me$_2$NC$_{12}$H$_{25}$	96	14 : 63 : 23
3	—	3	Me$_2$NC$_{12}$H$_{25}$	25	40 : 55 : 5
4	MeO(CH$_2$)$_2$OH	15	Me$_2$NC$_{12}$H$_{25}$	96	8 : 65 : 27
5	MeO(CH$_2$)$_2$OH	6	Me$_2$NC$_{12}$H$_{25}$	98	21 : 61 : 18
6	MeO(CH$_2$)$_2$OH	3	Me$_2$NC$_{12}$H$_{25}$	90	42 : 49 : 9
7	*i*BuCOMe	15	Me$_2$NC$_{12}$H$_{25}$	97	2 : 66 : 32
8	*i*BuCOMe	6	Me$_2$NC$_{12}$H$_{25}$	96	14 : 61 : 25
9	*i*BuCOMe	3	Me$_2$NC$_{12}$H$_{25}$	88	44 : 48 : 8
10	MeO(CH$_2$)$_2$OH	15	EtN(*i*Pr)$_2$	42	97 : 3 : 0
11	*i*BuCOMe	15	EtN(*i*Pr)$_2$	66	92 : 8 : 0
12	AcOEt	15	Me$_2$NC$_{12}$H$_{25}$	7	6 : 94 : 0

[a] Conditions: Pd(acac)$_2$ 4.4 × 10^{-5} mol; molar ratios: L-arabinose : amine : Pd : TPPTS = 150 : 150 : 1 : 3; 80 °C; 45 min; 1 g of L-arabinose in H$_2$O : cosolvent (0.5 mL : 1.25 mL). [b] GC evaluation. [c] 2% of tetraethers also identified.

Table 3 Recycling experiments in water using either $Me_2NC_{12}H_{25}$ or KF/Al_2O_3 as base

Run	Base	Cycle	Conv.[a] (%)	Ether selectivity[a] mono : di : tri (%)
1	$Me_2NC_{12}H_{25}$	1[b]	99	4 : 57 : 37
2	First reuse	2[c]	93	19 : 57 : 24
3	2nd reuse	3[c]	22	100 : 0 : 0
4	KF/Al_2O_3	1[d]	94	33 : 48 : 19
5	First reuse	2[e]	96	84 : 16 : 0
6	2nd reuse	3[e]	35	100 : 0 : 0

[a] GC evaluation. [b] Conditions: $Pd(acac)_2$ 4.4 × 10^{-5} mol; molar ratios: sugar : $Me_2NC_{12}H_{25}$: butadiene : Pd : TPPTS = 150 : 150 : 2250 : 1 : 3; 80 °C; 45 min; 1 g of L-arabinose in 0.5 ml H_2O. [c] Addition of sugar : amine : butadiene (150 : 150 : 2250; L-arabinose: 1 g) to the aqueous phase recovered from the above run. [d] Conditions: $Pd(acac)_2$ 4.4 × 10^{-5} mol; molar ratios: sugar : butadiene : Pd : TPPTS = 150 : 2250 : 1 : 3; 80 °C; 45 min; 1.21 g of KF/Al_2O_3, 1 g of L-arabinose in 0.5 ml H_2O. [e] Addition of sugar : butadiene (150 : 2250; L-arabinose: 1 g) to the aqueous suspension recovered from the above run.

use of methylisobutylketone as additive (entry 11). In this last case however, the monoether selectivity was enhanced (92% entry 11, compared to 79%, entry 9, Table 1, at about 65% conversion in both cases). Ethyl acetate was not suitable as a cosolvent in this telomerization reaction (entry 12).

Thus, only the selectivity towards the monopentosides could be improved by using a cosolvent such as methylisobutylketone associated with a crowded tertiary amine like $EtN(iPr)_2$. In the presence of dimethyldodecylamine, the use of a cosolvent was not beneficial for the mono or diether selectivities; the amphiphilic character of this amine favours mass transfer between the aqueous and organic phases, thus enhancing the reactivity of all potential substrates.

Recycling experiments

Since another advantage of the biphasic systems could be the immobilisation of the active catalyst, we looked for recycling possibilities. After one run using the conditions of entry 13, Table 1, we used ethyl acetate to separate the ethers from the aqueous phase. L-Arabinose, $Me_2NC_{12}H_{25}$ and butadiene were then added to the recovered aqueous phase and the mixture was heated at 80 °C for 45 min: the conversion was 93% but dropped to 22% for the second recycling (Table 3, runs 2 and 3). The drop in catalyst activity could be due to partial extraction of the active palladium species by the organic solvent. As a result, KF/Al_2O_3, a heterogeneous base, was used instead of $Me_2NC_{12}H_{25}$ since it has proven efficient for palladium catalysed reactions involving η^3-allylpalladium intermediates as in Tsuji–Trost[34,35] or telomerization reactions.[36] The first use of these heterogeneous conditions afforded a high conversion, comparable to the experiments with $Me_2NC_{12}H_{25}$ (runs 1 and 4), with different relative amount of monoethers. The catalyst activity was preserved for the first recycling experiment with an improvement in monoether selectivity (run 5). However, the second recycling experiment again led to a low conversion (run 6) which could be explained by partial destruction of the catalyst, since a precipitate of palladium black was observed.

Conclusion

The telomerization of butadiene with pentoses can be carried out in an aqueous medium using $Pd(acac)_2$–TPPTS as a catalytic precursor and a tertiary amine as a promoter. A simple variation of the experimental conditions allowed us to prepare two classes of surfactant molecules having a different hydrophilic–lipophilic balance. The choice of the amine was crucial with regard to the control of the octadienyl chain grafting. With a crowded amine like ethyldiisopropylamine, the monooctadienylpentosides were the major products, especially in the presence of isobutylmethylketone as cosolvent. With the amphiphilic dimethyldodecylamine, a second grafting occurred which afforded a mixture of diethers. Recycling experiments, still relatively inefficient, are in progress.

Experimental

The general procedure for telomerization and product analysis and the preparation of KF/Al_2O_3 have been described in our previous articles.[4,19,36] Distilled H_2O is used as the solvent. TPPTS was a gift from Rhodia. The following new products have been identified.

The IR and elemental analyses were performed on a mixture of dioctadienylethers of xylose:

FT-IR cm^{-1} 2930, 2859, 1747, 1438, 1370, 1229.

Anal. Calc. For $C_{25}H_{38}O_5$: C, 66.64; H, 8.50. Found C, 66.77; H, 8.69%.

GC-MS (IC, NH_4^+) *m*/*z* 468 (M+18, 60), 325 (M-125, 100).

[(2′-(*E*)-7′-Octadienyloxy)-2,3-di-*O*-acetyl-2-(2″-(*E*)-7″-octadienyl)]-β-D-xylopyranoside (2β)

$\delta^1_{\rm H}$ NMR ($CDCl_3$, 500 MHz) ppm 1.45 (4H, quint, $J_{5',4'} = J_{5',6'} = J_{5'',4''} = J_{5'',6''}$ 8.0 Hz, 5′-*H*, 5″-*H*), 1.95–2.15 (14H, m, –$COCH_3$, 4′*H*, 4″-*H*, 6′-*H*, 6″-*H*), 3.3 (2H, m, 5a-*H*, 2-*H*), 3.95–4.10 (3H, m, 1″b-*H*, 1′b-*H*, 1′a-*H*), 4.15–4.25 (2H, m, 1″a-*H*, 5e-*H*), 4.45 (1H, d, $J_{1,2}$ = 7 Hz, 1-*H*), 4.9 (1H, dd, $J_{4,5e}$ 6.0 Hz, $J_{5a,4}$ 11.0 Hz, 4-*H*), 4.95 (4H, m, 8′a-*H*, 8′b-*H*, 8″a-*H*, 8″b-*H*), 5.10 (1H, t, $J_{3,2} = J_{3,4}$ 8.5 Hz, 3-*H*), 5.40–5.90 (6H, m, 2′-*H*, 2″-*H*, 3′-*H*, 3″-*H*, 7′-*H*, 7″-*H*). $\delta^{13}_{\rm C}$ NMR ($CDCl_3$, 126 MHz) ppm 20.8, 20.9 (2 CH_3), 28.2 (5′-*C*, 5″-*C*), 31.6, 31.7, 33.2 (4′-*C*, 4″-*C*, 6′-*C*, 6″-*C*), 62.3 (5-*C*), 69.4 (4-*C*), 70.1 (1′-*C*), 72.9 (3-*C*), 73.0 (1″-*C*), 77.7 (2-*C*), 102.3 (1-*C*), 114.6 (8′-*C*, 8″-*C*), 125.6 (2′-*C*), 126.4 (2″-*C*), 134.5, 134.9 (3′-*C*, 3″-*C*), 138.5 (7′-*C*, 7″-*C*), 169.7, 170.1 (2 *C*O).

[(2′-(*E*)-7′-Octadienyloxy)-2,4-di-*O*-acetyl-3-(2″-(*E*)-7″-octadienyl)]-β-D-xylopyranoside (3β)

$\delta^1_{\rm H}$ NMR ($CDCl_3$, 500 MHz) ppm 1.50 (4H, m, 5′-*H*, 5″-*H*), 1.95–2.15 (14H, m, –$COCH_3$, 4′-*H*, 4″-*H*, 6′-*H*, 6″-*H*), 3.37

(1H, dd, $J_{5a,5e}$ 11.8 Hz, $J_{5a,4}$ 8.8 Hz, 5a-*H*), 3.55 (1H, t, $J_{1''b,1''a} = J_{1''b,2''}$ 12.0 Hz, 1″b-*H*), 4.02–4.25 (4H, m, 1′a-*H*, 1′b-*H*, 1″a-*H*, 5e-*H*), 4.50 (2H, t, $J_{1,2} = J_{3,2} = J_{3,4}$ 7.0 Hz, 1-*H*, 3-*H*), 4.95–5.05 (6H, m, 2-*H*, 4-*H*, 8′a-*H*, 8′b-*H*, 8″a-*H*, 8″b-*H*), 5.48–5.90 (6H, m, 2′-*H*, 2″-*H*, 3′-*H*, 3″-*H*, 7′-*H*, 7″-*H*). $\delta^{13}{}_{C}$ NMR ($CDCl_3$, 126 MHz) ppm 20.9 (2 CH_3), 28.1 (5′-*C*, 5″-*C*), 31.6, 33.1 (4′-*C*, 4″-*C*, 6′-*C*, 6″-*C*), 65.2 (5-*C*), 68.8 (1′-*C*), 69.9 (4-*C*), 70.7 (2-*C*), 71.9 (1″-*C*),75.8 (3-*C*), 98.3 (1-*C*), 114.6 (8′-*C*, 8″-*C*), 125.4 (2′-*C*), 126.1 (2″-*C*), 134.8 (3′-*C*, 3″-*C*), 138.5 (7′-*C*, 7″-*C*), 169.7, 169.9 (2 *C*O).

[(2′-(*E*)-7′-Octadienyloxy)-2,3-di-*O*-acetyl-4-(2″-(*E*)-7″-octadienyl)]-β-D-xylopyranoside (4β)

$\delta^{1}{}_{H}$ NMR ($CDCl_3$, 500 MHz) ppm 1.45 (4H, quint, $J_{5',4'} = J_{5',6'} = J_{5'',4''} = J_{5'',6''}$ 8.0 Hz, 5′-*H*, 5″-*H*), 1.95–2.15 (14H, m, –COCH_3, 4′-*H*, 4″-*H*, 6′-*H*, 6″-*H*), 3.25 (1H, dd, $J_{5a,5e}$ 11.8 Hz, $J_{5a,4}$ 10.8 Hz, 5a-*H*), 3.55 (1H, m, 1″b-*H*), 4.02–4.25 (5H, m, 1′a-*H*, 1′b-*H*, 1″a-*H*, 4-*H*, 5e-*H*), 4.45 (2H, d, $J_{1,2}$ 7 Hz, 1-*H*), 4.95–5.10 (5H, m, 2-*H*, 3-*H*, 8′a-*H*, 8′b-*H*, 8″a-*H*, 8″b-*H*), 5.40–5.90 (6H, m, 2′-*H*, 2″-*H*, 3′-*H*, 3″-*H*, 7′-*H*, 7″-*H*). $\delta^{13}{}_{C}$ NMR ($CDCl_3$, 126 MHz) ppm 20.7, 20.8 (2CH_3), 28,1 (5′-*C*, 5″-*C*), 31.5, 33.1 (4′-*C*, 4″-*C*, 6′-*C*, 6″-*C*), 63.6 (5-*C*), 69.6 (1′-*C*), 71.4 (2-*C*), 71.7 (1″-*C*),73.7 (3-*C*), 74.2 (4-*C*), 99.6 (1-*C*), 114.6 (8′-*C*, 8″-*C*), 125.4 (2′-*C*), 126.0 (2″-*C*), 134.9 (3′-*C*, 3″-*C*), 138.4 (7′-*C*, 7″-*C*), 169.7, 170.1 (2 *C*O).

Acknowledgements

This work was supported by the "Contrat d'objectifs" in "Europol'Agro" framework (Glycoval program). We are grateful to the public authorities of Champagne Ardenne for a fellowship to B. E. and material funds and to Dr Karen Plé for linguistic improvement of the manuscript.

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Synthesis of 3-(4-*tert*-butylphenyl)-2-propen-1-one, a precursor to Lilial®, *via* an aldol condensation in an ionic liquid

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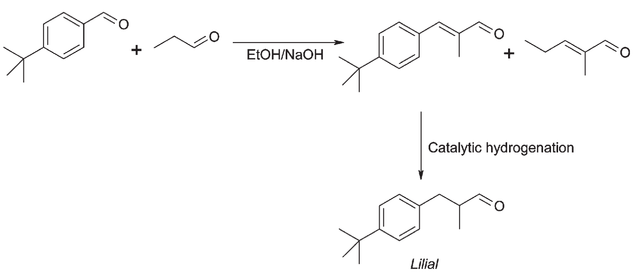
Received 19th October 2004, Accepted 1st March 2005
First published as an Advance Article on the web 15th March 2005
DOI: 10.1039/b416021e

An efficient synthesis of a precursor to Lilial®, based on an aldol condensation in an ionic liquid, is described, utilising piperidine as the base catalyst. The yields obtained with this methodology are significantly increased in comparison with those reported in organic solvents to date. In the ionic liquid, the self-aldol condensation of propanal is suppressed and leads to an increased selectivity with respect to the cross-aldol condensation product without the need to use an excess of 4-*tert*-butylbenzaldehyde to obtain high selectivities.

Introduction

Lilial®[1] is a fragrance and a precursor to the fungicide, Fenpropimorph.[2] It is produced industrially[1] *via* a cross-aldol condensation using 4-*tert*-butylbenzaldehyde and propanal followed by a catalytic hydrogenation, Scheme 1. Conventional cross-aldol reactions suffer from moderate yields due to self-condensation reactions, in this instance the formation of 2-methyl-2-pentenal can occur. Unless the 4-*tert*-butylbenzaldehyde is in a large excess, it is impossible to increase conversions without forming increasing concentrations of 2-methyl-2-pentenal waste. The commercial process for Lilial® avoids self-aldol condensation reactions, and subsequent workup problems, by using an excess of 4-*tert*-butylbenzaldehyde (1.5 fold molar excess with respect to the propanal) with aqueous NaOH as the catalyst. In order to obtain the high selectivity, the conversion is restricted to <60%. This is a low atom efficiency process and due to the high cost of the 4-*tert*-butylbenzaldehyde, efficient recycling of the unreacted starting material is required.

Conventionally, aldol condensation reactions are performed in organic solvents, such as methanol or ethanenitrile; however, recently, it has been reported that ionic liquids can also provide a useful aldol reaction media.[3–6] The interest in ionic liquids is due to the ability to tune the physical properties of the solvent systematically, for example the density, viscosity and water miscibility. In addition, due to their very low vapour pressures, reactive chemistry and the workup thereof may be performed without the production of VOCs.[7] The range of reactions performed in ionic liquids is extensive and includes alkylations,[8] C–C bond coupling reactions,[9–11] polymerisations,[12–14] hydrogenations,[15–17] hydroformylations,[14] and alkoxycarbonylations.[18] These reactions have been extensively reviewed recently.[19]



Scheme 1 Industrial reaction to form Lilial® *via* the aldol condensation of 4-*tert*-butylbenzaldehyde with propanal yielding 3-(4-*tert*-butyl-phenyl)-2-methyl-propenal.

The self-aldol condensation of propanal and crossed aldol condensation of propanal with 2-methylpentanal in a range of ionic liquids, including [C_4mim][PF_6] and [C_6mim][BF_4], at 80–100 °C has been reported by Mehnert *et al.*,[20] in which NaOH was used as the base in the form of solid particles. Increased yields of oligomers $>C_9$ were found compared with molecular solvents. Asymmetric aldol condensations have also been reported in ionic liquids.[4,5] For example, using propanone and a range of aromatic and aliphatic aldehydes, enantiomeric excesses (ee's) up to 89% were observed at high conversion with L-proline.[5] In addition, little loss in activity or ee was observed on recycle of the catalyst–ionic liquid system. Supported ionic liquids have also been used to promote aldol condensations. Abelló *et al.* have demonstrated that cholinium hydroxide supported on magnesia is highly effective for a range of aldol condensations converting both aldehydes and ketones.[21] The use of dimethylammonium dimethylcarbamate has been reported (as a distillable, ionic medium) for similar aldol condensations by Kreher *et al.*[22] For the reaction of benzaldehyde with propanal, yields of 61% after 25 h at 50 °C were obtained. In general, however, the selectivity with respect to the cross-aldol product compared with the self-condensation products, in particular that of propanal, is not addressed in these studies.

We describe here the use of a range of catalysts in ionic liquids and molecular solvents for the aldol condensation of 4-*tert*-butylbenzaldehyde and propanal. In particular, the effect of the ionic liquid on the selectivity with respect to the formation of 2-methyl-2-pentenal is discussed.

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Experimental

Unless otherwise stated all reagents (Aldrich) were used as received. The ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate ([C$_4$mim][BF$_4$]), 1-ethyl-3-methylimidazolium ethylsulfate ([C$_2$mim][EtSO$_4$]), 1-butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}amide ([C$_4$mim][NTf$_2$]), 1-butyl-2,3-dimethylimidazolium bis{(trifluoromethyl)sulfonyl}amide ([C$_4$dmim][NTf$_2$]), 1-butyl-1-methylpyrolidinium bis{(trifluoromethyl)sulfonyl}amide ([bmpyrr][NTf$_2$]), triethylhexylammonium bis{(trifluoromethyl)sulfonyl}amide ([N$_{2,2,2,6}$][NTf$_2$]), methyltrioctylammonium bis{(trifluoromethyl)sulfonyl}amide ([N$_{1,8,8,8}$][NTf$_2$]) were prepared in house using standard literature methods.[23–25] Trihexyltetradecylphosphonium bis{(trifluoromethyl)sulfonyl}amide ([P$_{6,6,6,14}$][NTf$_2$]) and 1-ethyl-3-methylimidazolium trifluorotris(perfluoroethyl)phosphate ([C$_2$mim][FAP]) were supplied by Cytec and Merck, respectively. All [NTf$_2$]$^-$ and [FAP]$^-$ ionic liquids contained <0.2 wt% water determined by Karl–Fischer analysis. [C$_4$mim][BF$_4$] and [C$_2$mim][EtSO$_4$] contained 0.70 wt% and 0.66 wt% water, respectively. The hydrotalcite catalyst was prepared using the method reported by Roelofs *et al.* from an aqueous solution of Mg(NO$_3$)$_2$·6H$_2$O and Al(NO$_3$)$_3$·9H$_2$O in a 2 : 1 mole ratio.[26] The BET surface area of the material formed was 200 m^2 g^{-1} and the XRD pattern is in agreement with that reported previously.[26]

Typically, the aldol experiments were carried out in a sealed flat-bottomed flask (12 cm^3) using solvent (2 cm^3), catalyst (5 mmol), and 4-*tert*-butylbenzaldehyde (10 mmol) at 20 °C and stirred at 1000 rpm, unless otherwise stated. Propanal (15 mmol) was added in 8 aliquots, each added slowly over 5 min *via* a rubber septum. After the addition of each aliquot, the reaction mixture was stirred for 1 h to ensure that the reaction had proceeded to completion. The first aliquot was added at the same time as the addition of the 4-*tert*-butylbenzaldehyde to the catalyst–ionic liquid solution in order to ensure good mixing was achieved. For reactions using NaOH and L-proline, the catalysts were pre-dissolved by heating at 65 °C for 30 min prior to use. For the supported catalyst studies, the reactions were carried out in a Baskerville mini-autoclave at 65 and 100 °C; silica-supported piperidine (2.5 g; 2 mmol g^{-1}; 5 mmol piperidine equivalent) and hydrotalcite (2 g; calcined at 500 °C for 16 h prior to reaction) were used.

The reaction products were analysed by GC, and ^{1}H and ^{13}C NMR spectroscopy. NMR spectra at room temperature were performed on a Bruker Advance DRX 500 MHz NMR spectrometer. GC samples were analysed using a Hewlett Packard 6890 GC fitted with an RTX-5 column (30 m, 0.25 μm diameter) and a flame ionisation detector. The retention time of the peaks were compared against authentic samples. In the case of organic solvents, samples were analysed directly. When ionic liquids were used, the samples were extracted using cyclohexane in a volume ratio 1 : 5 (IL : cyclohexane), repeated four times, then the extracted phase samples combined and analysed. In all reactions, the NMR and GC analyses showed comparable results.

Throughout the paper, the selectivity is defined as:

$$\text{selectivity} = 100(\text{cross-aldol product})/\{(\text{self-aldol product}) + (\text{cross-aldol product})\}$$

The conversions are defined as:

$$\text{conversion} = 100(\text{cross-aldol product})/\{(\text{benzaldehyde}) + (\text{cross-aldol product})\}$$

with respect to the formation of the cross-aldol product and:

$$\text{conversion} = 100(\text{self-aldol product})/\{(\text{propanal}) + (\text{self-aldol product}) + (\text{cross-aldol product})\}$$

with respect to the formation of the self-aldol product.

The characterisation of 3-(4-*tert*-butyl-phenyl)-2-methylpropanal yielded:

^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 1.39 (s, 9H, –CCH_3); 2.13 (s, 3H, –CHCCH_3CHO); 7.28 (s, 1H, –CHCCH$_3$CHO); 7.49–7.56 (m, 4H, aromatic); 9.61 (s, 1H, –CHCCH$_3$CHO). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 11.4; 31.6; 35.3; 126.1; 103.5; 132.8; 138.0; 150.3; 153.6; 196.1. $\nu_{\max}$/cm^{-1} (KBr) 2960 (s), 1674 (s), 1606 (s). Melting point: 69–71 °C.

Results and discussion

Table 1 summarises the results from a range of supported and homogeneous catalysts commonly used in aldol condensations[27–29] for the reaction of 4-*tert*-butylbenzaldehyde with propanal in [C$_4$dmim][NTf$_2$]. It is clear that, in the ionic liquid, the use of piperidine as the catalyst at room temperature gives the highest conversion whilst maintaining a high selectivity. Although good conversions were obtained with piperizine, morpholine and NaOH, for example, much lower selectivities were observed. For direct comparison with the results from the piperidine reactions, the concentration of the piperizine catalyst was halved to allow for the fact that piperizine is a diamine. It is noticeable that the conversion increases despite the lower catalyst concentration, due to a mass transfer effect. In many of the ionic liquid reactions a fine precipitate is formed on the addition of the catalyst to the 4-*tert*-butylbenzaldehyde solution. With piperidine, the solution may be stirred easily; however, at the higher concentration of piperizine, the precipitate prevents good mixing and reduces the conversion. In contrast, L-proline catalysed the self-aldol reaction in preference to reaction with 4-*tert*-butylbenzaldehyde and no reaction was observed with 2,2′,6,6′-tetramethylpiperidine.

The conversion to 3-(4-*tert*-butyl-phenyl)-2-methylpropenal using the combination of piperidine and [C$_4$dmim][NTf$_2$] is also significantly better than that reported for the industrial process.[1] Table 1 shows the results from the reaction performed in aqueous methanol using NaOH. In agreement with the yields reported for the industrial process, yields of only 55% were obtained, even with an excess of 4-*tert*-butylbenzaldehyde. It should be noted that using this solvent–catalyst combination, if the propanal is used in excess, only the self-aldol condensation occurs.

The homogeneous catalysts were far superior to the supported heterogeneous catalysts, hydrotalcite and silica-supported piperazine. Both catalysts were inactive at room temperature and at 65 °C. This is probably due to poor mass transport to the active catalytic sites. Although some activity was observed at higher temperatures (100 °C), similar activity

Table 1 Comparison of the catalyst on the conversion and selectivity with respect to the formation of 3-(4-*tert*-butyl-phenyl)-2-methyl-propenal following the addition of propanal (15 mmol) to 4-*tert*-butylbenzaldehyde (10 mmol)

Catalyst/solvent	Temp./°C	Conversion (%)	Selectivity (%)
Piperazine/[C_4dmim][NTf_2]	20	50	75
Piperazine[a]/[C_4dmim][NTf_2]	20	60	62
Piperidine/[C_4dmim][NTf_2]	20	97	84
2-Methylpiperidine/[C_4dmim][NTf_2]	20	50	94
2-Ethylpiperidine/[C_4dmim][NTf_2]	20	50	96
2,2′,6,6′-Tetramethylpiperidine/[C_4dmim][NTf_2]	20	0	—
Morpholine/[C_4dmim][NTf_2]	20	64	71
2,6-Dimethylmorpholine/[C_4dmim][NTf_2]	20	84	85
L-Proline/[C_4dmim][NTf_2]	20	5	66
NaOH/[C_4dmim][NTf_2]	20	40	62
Supported piperazine/[C_4dmim][NTf_2]	100	5	62
Hydrotalcite/[C_4dmim][NTf_2]	100	12	71
NaOH/MeOH[b]	20	55	100

[a] 2.5 mmol catalyst. [b] 0.1 g of 35% NaOH–H_2O solution in 3.7 g MeOH with 0.03 mol 4-*tert*-butylbenzaldehyde and 0.02 mol propanal.[1]

was observed for both the cross-aldol and self-aldol reactions, which resulted in poor selectivities.

The effects of the cation and anion of the ionic liquid were investigated and the results are summarised in Table 2 and Fig. 1. Whilst the cation had little effect on the reaction, the anion had a significant influence. For water-miscible ionic liquids such as [C_4mim][BF_4] and [C_2mim][$EtSO_4$], increased conversion to 2-methyl-2-pentenal was observed, which results in lower conversions. In contrast, in [NTf_2]$^-$ and [FAP]$^-$ ionic liquids, the reaction proceeded with both high yield and selectivity. For both anions, selectivities close to 100% were found with the range of cations if the conversion is limited to 80%.

Fig. 2 shows a comparison of the formation of the cross-aldol and self-aldol condensation products and the selectivity as a function of added propanal in a range of organic solvents, under solventless conditions and in [bmpyrr][NTf_2]. It is clear that with increasing polarity of the molecular solvent, the conversion and selectivity towards the cross-aldol product increases. However, even in methanol, the self-aldol condensation reaction proceeds despite the presence of a large excess of 4-*tert*-butylbenzaldehyde, *i.e.* at conversions <30%. In comparison, using [bmpyrr][NTf_2] significantly suppresses the self-aldol reaction of propanal until approximately 80% of the 4-*tert*-butylbenzaldehyde has reacted. Similar variations were found for all the [NTf_2]$^-$ based ionic liquids studied.

Table 2 Comparison of the effect of ionic liquid on the conversion and selectivity with respect to the formation of 3-(4-*tert*-butyl-phenyl)-2-methyl-propenal following the addition of propanal (15 mmol) to 4-*tert*-butylbenzaldehyde (10 mmol) using 5 mmol piperidine at 20 °C

Ionic liquid	Conversion (%)	Selectivity (%)
[C_4dmim][NTf_2]	98	84
[bmpyrr][NTf_2]	97	81
[$P_{6,6,6,14}$][NTf_2]	95	74
[$N_{2,2,2,6}$][NTf_2]	97	74
[$N_{1,8,8,8}$][[NTf_2]	99	74
[C_4mim][NTf_2]	99	85
[C_2mim][FAP]	99	78
[C_4mim][BF_4]	71	64
[C_2mim][$EtSO_4$]	52	44

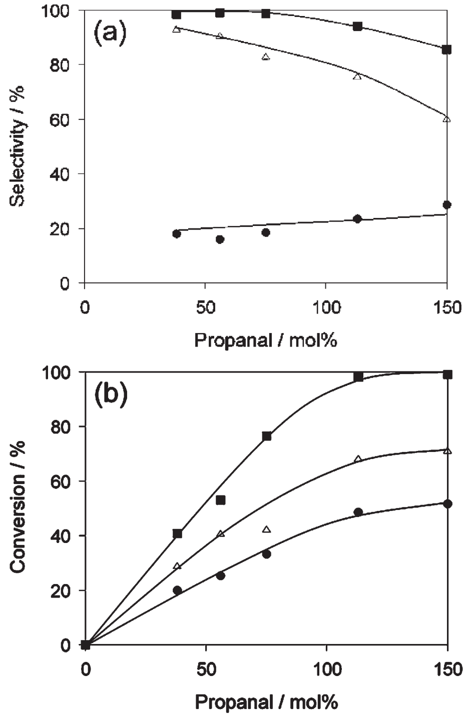

Fig. 1 Comparison of the effect of ionic liquid [C_4mim][FAP] (■), [C_4mim][BF_4] (△) and [C_2mim][$EtSO_4$] (●) on (a) selectivity and (b) conversion with respect to the formation of 3-(4-*tert*-butyl-phenyl)-2-methyl-propenal as a function of the addition of propanal to 4-*tert*-butylbenzaldehyde at 20 °C using piperidine as the catalyst.

With the anion having a significant effect on the selectivity of the cross-aldol reaction, it is important to know the effect of halide impurities present in the ionic liquid. Halide impurities occur as a result of an incomplete anion exchange during the metathetic step in the ionic liquid synthesis.[30] Although the residual halide may be washed out with water, this step is labour intensive, time consuming and, therefore, expensive. The effect of chloride ions present in the [C_4dmim][NTf_2] was investigated by spiking the ionic liquid with 25 ppm [C_4dmim]Cl. A decrease in selectivity from 84% to 67% was observed after the addition of 15 mmol propanal; however, the conversion was not affected significantly. This is in agreement

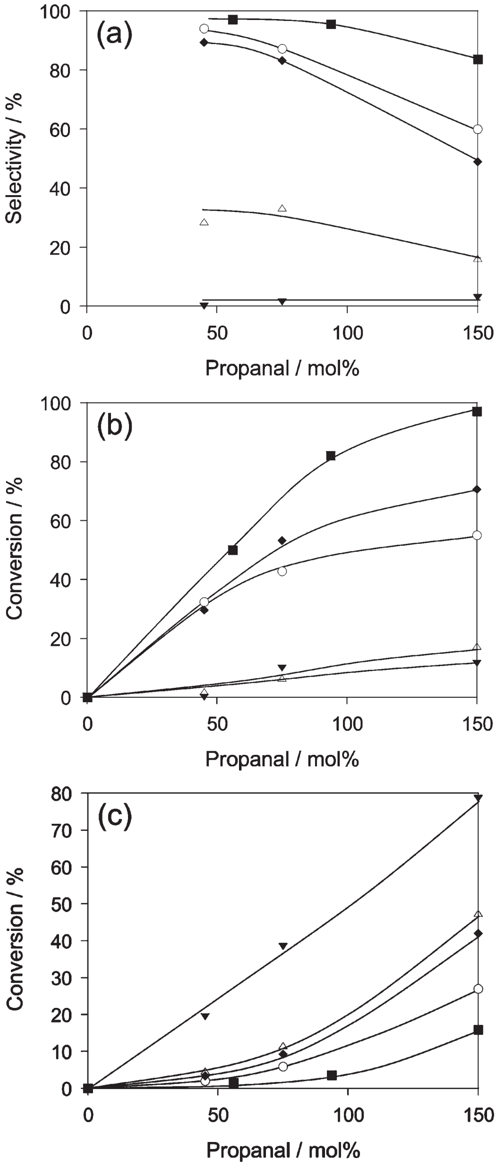

Fig. 2 Comparison of the effect of solvent media methanol (○), no solvent (△), cyclohexane (▼), ethanenitrile (◆) and $[C_4mpyr][NTf_2]$ (■) on (a) selectivity and (b) conversion with respect to 3-(4-*tert*-butylphenyl)-2-methyl-propenal, and (c) conversion with respect to 2-methyl-2-pentenal as a function of the addition of propanal to 4-*tert*-butylbenzaldehyde at 20 °C using piperidine as the catalyst.

with the results from the $[BF_4]^-$ and $[EtSO_4]^-$ ionic liquids which showed a decrease in the selectivity as the hydrophobicity decreased. It should be noted that the low selectivities for these ionic liquids are not likely to be due to residual halide. A halide-free synthesis was used to prepare $[C_2mim][EtSO_4]$ and the chloride content of $[C_4mim][BF_4]$ was measured as 0.74 ppm using cathodic stripping voltammetry.[31]

The precipitate which is formed on addition of the catalyst to the 4-*tert*-butylbenzaldehyde in the $[NTf_2]^-$ and $[FAP]^-$ ionic liquids is thought to be the formation of an iminium species. The mechanism of the aldol condensation is well known, and involves an equilibrium reaction of the secondary amine with the aldehyde, in this case 4-*tert*-butylbenzaldehyde, forming an iminium species.[32] The iminium species is more electrophilic than the original aldehyde and reacts with the enol form of the propanal forming the cross-aldol product. Diffuse reflectance IR spectra of the precipitate show bands at 1590 cm^{-1} corresponding to the ν(C=N) stretch and only a small feature at 1709 cm^{-1} associated with ν(C=O) from the aldehyde, in agreement with the iminium mechanism.[33] Furthermore, electrospray mass spectrometry of the solid shows a parent ion at an $(m/z)^+$ of 230. This corresponds to the mass of the iminium cation shown in Fig. 3. One possible explanation for the increased selectivity in the ionic liquids is that the formation of the precipitate drives all the piperidine into the iminium form and, therefore, there is no free base to catalyse the self-aldol process. The precipitate is soluble in propanal and, on addition of propanal, the solid partially dissolves and reacts to form the cross-aldol product only.

In contrast, although the solution becomes cloudy for reactions performed in $[C_2mim][EtSO_4]$ (which is similar to solventless conditions, but less than for $[C_4mim][BF_4]$), there is significantly less precipitate formed than in the $[NTf_2]^-$ and $[FAP]^-$ ionic liquids studied. In addition, little precipitate was observed in cyclohexane, ethanenitrile or methanol. ^1H NMR spectra of the *in situ* and pre-formed iminium species in $CDCl_3$ and CD_3CN showed that the equilibrium lies towards the free base and aldehyde; only the peak for the 4-*tert*-butylbenzaldehyde was observed, whereas if a significant concentration of the iminium species was present, a signal at δ ~8.6 ppm should also be observed.[34] Therefore, for solvents where the iminium species is soluble, the piperidine can catalyse either the self-aldol or cross-aldol reactions, which reduces the selectivity. This explanation is also consistent with the observation that little precipitate is formed in $[C_4dmim][NTf_2]$ using L-proline as the catalyst, and low selectivity was found. The solubility of the iminium species in this case may be the result of zwitterion formation in proline on addition of the aldehyde. In the case of 2,2′,6,6′-tetramethylpiperidine, the low activity is possibly due to steric hindrance around the nitrogen which prevents the formation of the iminium species and prevents reaction. Clearly, the position of the equilibria will shift as the 4-*tert*-butylbenzaldehyde is consumed and, hence, as the reaction proceeds, the concentration of piperidine in solution becomes greater and the formation of self-aldol product increases. By using the ionic liquid, similar selectivities to those found in the industrial process are observed, but coupled with high conversions without the need to use a large excess of 4-*tert*-butylbenzaldehyde.

To test the ionic liquid mechanism proposed above, the reaction was performed as a function of the initial piperidine concentration. As expected, the formation of 2-methyl-2-pentenal was found to increase significantly with increasing piperidine concentration, Fig. 4. With higher amounts of

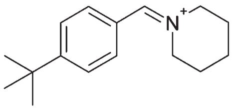

Fig. 3 Iminium cation formed due to the reaction of 4-*tert*-butylbenzaldehyde with piperazine.

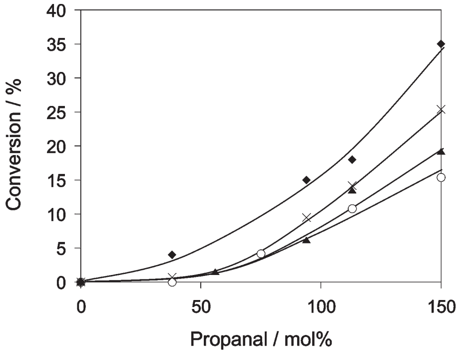

Fig. 4 Comparison of the concentration of piperidine 40 mol% (○), 50 mol% (▲), 70 mol% (×) and 100 mol% (◆) on conversion with respect to 2-methyl-2-pentenal as a function of the addition of propanal to 4-*tert*-butylbenzaldehyde at 20 °C.

piperidine, the conversion at which the catalyst concentration exceeds the 4-*tert*-butylbenzaldehyde concentration decreased and the reaction became less selective at the higher conversions.

The high selectivity found in the $[NTf_2]^-$ and $[FAP]^-$ ionic liquids is still observed, even at low volumes of ionic liquid. For example, selectivities of 81%, at 97% conversion, and 80%, at 94% conversion, were found using 0.25 cm^3 and 2 cm^3 of $[bmpyrr][NTf_2]$, respectively, with 4-*tert*-butylbenzaldehyde (1.6 cm^3; 10 mmol) and piperidine (0.5 cm^3). Therefore the rôle of the ionic liquid may be to simply increase the ionic atmosphere of the reaction mixture and thus shift the equilibrium to the iminium species which is not very soluble in the 4-*tert*-butylbenzaldehyde and precipitation occurs. As described above, the precipitation process shifts the equilibrium further to the iminium species by removing it from solution. Since this is viable even with small concentrations of ionic liquid, it is possible to use the ionic liquid as an additive.

Similar selectivities are also obtained using 4-methylbenzaldehyde and 4-isopropylbenzaldehyde; 93% and 92% selectivity at 90% conversion for the cross-aldol reaction with propanal (using piperidine in $[C_4dmim][NTf_2]$) was observed, respectively. As found with 4-*tert*-butylbenzaldehyde, a precipitate is formed on the addition of piperidine.

In many reactions, recycle of the ionic liquid is achieved using solvent extraction with, for example, diethyl ether or hexane. Similarly, in the present study, after extraction with cyclohexane, the ionic liquid was recovered and the reaction was repeated. However, during the extraction, piperidine was leached from the ionic liquid phase. The leached catalyst was recoverable from the product by distillation. After extraction with diethyl ether, the ionic liquid, reagents and catalyst were added as for the original reaction which resulted in a selectivity of 90% and a conversion of 95%. Although the ionic liquid could be recycled, this uses a volatile organic solvent to recycle the ionic liquid and, therefore, limits its impact as a clean solvent. In these reactions, it is possible to separate the ionic liquid from the product by filtration as 3-(4-*tert*-butylphenyl)-2-methyl-propenal is insoluble. After filtration and purification by recrystallisation from hexane, an isolated yield of 75% was obtained. The fact that the product is insoluble in the ionic liquid also decreases the possibility of further aldol condensation reactions occurring with the product decreasing the selectivity further.

Conclusions

Ionic liquids based on $[NTf_2]^-$ and $[FAP]^-$ have been shown to provide an efficient media in which to perform the aldol condensation of 4-*tert*-butylbenzaldehyde and propanal to form 3-(4-*tert*-butyl-phenyl)-2-methyl-propenal, using piperidine. Significantly higher selectivities are found at high conversions of the 4-*tert*-butylbenzaldehyde compared with either the industrial process or using piperidine in molecular solvents. The higher selectivities in the ionic liquid system appear to be related to the formation of an insoluble iminium species which reduces the concentration of free catalyst available for reaction and prevents catalysis of the self-aldol condensation. The low solubility of the final product allows ease of recycle of the ionic liquid and prevents further reaction.

Acknowledgements

The authors wish to thank the EPSRC manufacturing molecule initiative (MMI) for funding this project under grant GR/S19219 and DELNI (AMcK). David Milroy is thanked for preparing the hydrotalcite catalyst, and Cytec and Merck for the generous gift of some ionic liquids.

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Kinetics of single- and two-phase synthesis of the ionic liquid 1-butyl-3-methylimidazolium chloride

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Received 9th November 2004, Accepted 4th March 2005
First published as an Advance Article on the web 15th March 2005
DOI: 10.1039/b417124a

The kinetics of the synthesis of the ionic liquid 1-butyl-3-methylimidazolium chloride (IL) from 1-methylimidazole (MIM) and 1-chlorobutane (Cl-Bu) were studied in a batch reactor. For a MIM-conversion >8%, neat synthesis leads to two phases either rich in IL or Cl-Bu, whereby MIM is soluble in both phases. Addition of ethanol (>20 vol%) leads to a single-phase synthesis and to an increase of the effective rate constant by IL-formation (salt effect). The agreement of the measured and calculated synthesis progress is sufficient in both cases; modelling is based on the experimentally determined thermodynamic and kinetic data. Surprisingly, the rates of single-phase (20 vol% ethanol) and (stirred) two-phase synthesis are almost the same which is the result of the counterbalance of the salt effect (favouring single-phase synthesis) and the higher reactant concentrations (favouring neat synthesis). So for industrial production, the latter synthesis mode is advantageous, as solvent separation is not required. Finally, with respect to a continuous synthesis, the (neat) synthesis was successfully conducted in a tubular reactor.

Introduction

Ionic liquids (ILs) are low melting salts (<100 °C) with negligible vapour pressure and represent a new and promising solvent class, particularly with regard to homogeneous two-phase catalysis[1–3] and extractions.[4–6] The high potential of ionic liquids will probably lead to an increasing demand. Currently ILs are mainly produced in batch reactors and various companies already supply ILs; however, at comparatively high prices. The production costs will largely depend on the scale and on the type of reactor, whereby a continuous synthesis is certainly advantageous compared to a batch process.

For the design of technical reactors, kinetic data are needed. As shown in this paper, IL-synthesis is often complicated by the formation of two phases, at least without addition of a solvent. In the neat two-phase system, mass transfer and the partition of components in both phases have to be considered. For single phase synthesis this is by nature not required, but then the solvent and the increasing ion concentration (salt effect) may influence the kinetics.[7]

Up to now, kinetic data such as reaction order(s), rate constants as well as activation energies have not been published and to the best of our knowledge the kinetics of IL-synthesis have not been characterised with the exception of two (qualitatively orientated) studies on the influence of microwaves on the synthesis time in the case of dialkylimidazolium halides.[8,9]

As a contribution to a better understanding of the kinetics of IL-synthesis and to the development of an efficient (continuous) process, the synthesis of 1-butyl-3-methylimidazolium chloride was studied as an instructive example. [BMIM]Cl is a bulk IL and a source for various other ILs, formed by the reaction of 1-methylimidazole (MIM) and 1-chlorobutane (Cl–Bu)[10] (Fig. 1).

Results and discussion

The kinetic studies were carried out in a batchwise-operating stirred lab-scale glass reactor. The two liquid reactants MIM and Cl-Bu were mixed (together with ethanol as a solvent in the case of single-phase synthesis) and the conversion was monitored at constant temperatures. Cl-Bu was used in excess, typically 1.4 mol per mol MIM, as the separation of Cl-Bu (boiling point T_b = 79 °C at 1 bar) from the synthesised IL is much easier than the one of MIM (T_b = 198 °C). Thermal effects during the exothermic synthesis can be neglected (reaction time > 1 d); therefore, the synthesis was always conducted under isothermal conditions. In addition to the kinetic measurements, the phase behaviour of the system MIM–Cl-Bu–[BMIM]Cl during neat synthesis was studied. Details of the experimental procedure and analysis are provided at the end of this paper.

Phase behaviour during neat [BMIM]Cl-synthesis

In the case of neat IL-synthesis (without solvent), two phases are formed for a MIM-conversion of more than about 8%. The respective triangular phase diagram for 70 °C is shown in Fig. 2. The reaction progress is depicted by the change of the composition with time (every 10 h), indicating that the synthesis is slow, *e.g.* 50 h are needed to reach 90% MIM-conversion. Acceleration of the rate by increasing the temperature is limited, as MIM then starts to decompose which leads to contamination and colours the IL. The two-phase

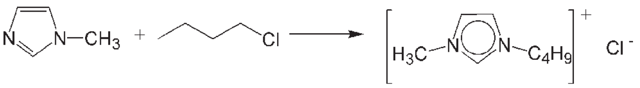

Fig. 1 Synthesis of 1-butyl-3-methylimidazolium chloride [BMIM]Cl.

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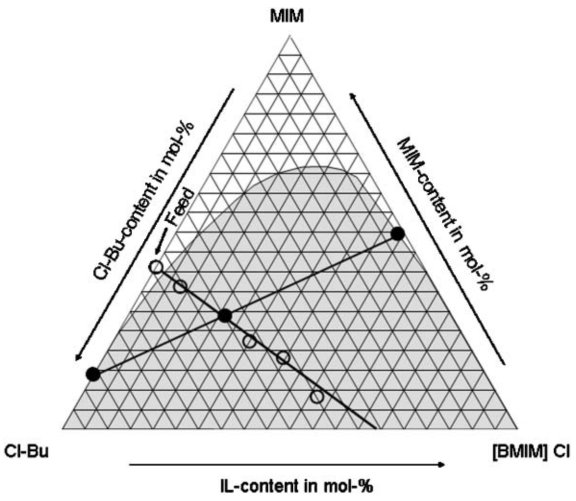

Fig. 2 Triangular phase diagram of the system [BMIM]Cl, Cl-Bu and MIM (period between two points: 10 h; $c_{\mathrm{MIM},0}$ = 4.12 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu},0}$ = 6.45 mol l^{-1}, T = 70 °C, stirred; grey area: two phases, white area: single-phase region).

behaviour is exemplarily shown by one tie-line (for t = 20 h). An IL-rich and a Cl-Bu-rich phase are formed, whereby (only) MIM is dissolved in both phases. The solubility of Cl-Bu in the IL is negligible and so one partition coefficient K for MIM can be used to describe the overall phase behaviour. The IL-phase, consisting of [BMIM]Cl and dissolved MIM, can be regarded as the *passive phase* with respect to the synthesis, and the reaction only takes place in the second phase consisting of MIM and Cl-Bu, denoted here as the *reaction phase* (index rp).

This two-phase behaviour of the synthesis of [BMIM]Cl can only be avoided by the addition of a solvent. For ethanol as the solvent, 20 vol% is required to ensure a single-phase synthesis. Although this approach is unfavourable for a technical synthesis with respect to the separation of IL and solvent, the single-phase synthesis was also investigated here in order to allow for a better understanding of the kinetics in general. In the following, the kinetics of both the single- and the two-phase synthesis will be discussed.

Kinetics of single-phase [BMIM]Cl-synthesis

The synthesis of [BMIM]Cl is a second order reaction overall, *i.e.* the rate is 1st order both with respect to MIM and Cl-Bu, as determined by variation of the initial concentrations of both reactants (details are given in ref. 11). In general, the rate in a batch reactor is independent of single or two-phase and is given by:

$$-\frac{\mathrm{d}n_{\mathrm{MIM}}}{\mathrm{d}t}=\frac{\mathrm{d}n_{IL}}{\mathrm{d}t}=k_{\mathrm{eff}}\times c_{\mathrm{Cl\text{-}Bu,rp}}\times c_{\mathrm{MIM,rp}}\times V_{\mathrm{rp}} \qquad (1)$$

with

n_i: amount of reactant i (mol),

k_{eff}: effective rate constant (m^3 mol^{-1} s^{-1}; see comments below for details),

$c_{i,\mathrm{rp}}$: concentration of i (mol m^{-3}),

V_{rp}: volume of reaction phase, total volume in case of single-phase synthesis (m^3).

For the single-phase synthesis, the mass balances of MIM and Cl-Bu and the introduction of the MIM-conversion X leads to the conversion rate:

$$\frac{\mathrm{d}X}{\mathrm{d}t}=k_{\mathrm{eff}}(1-X)(c_{\mathrm{Cl\text{-}Bu},0}-Xc_{\mathrm{MIM},0}) \qquad (2)$$

with $c_{i,0}$: initial concentration of reactant i (mol m^{-3}).

The ion concentration steadily increases during single-phase synthesis. According to Brønsted, ionic reactions are accelerated in an ionic environment if the activation step is accompanied by increasing electrical charges of the reactants.[7,12] For a charge separation during formation of a salt (here the IL) from non-ionic reactants (MIM and Cl-Bu), the coulombic interactions and the solvation of ions lead to an increase of the effective rate constant k_{eff}.[13] For [BMIM]Cl-synthesis, k_{eff} increases with conversion X and IL-concentration, respectively, by up to a factor of 10 (Fig. 3). The rate constant k_{eff} was determined according to eqn. (2) and the slope of $X(t)$ at different stages of the synthesis, respectively. In addition, the initial conversion rates of experiments starting with mixtures of MIM, Cl-Bu, and IL were measured. The results of both methods—shown in Fig. 3 as the ratio of k_{eff} to the initial value k_0 (at t = 0 and $c_{[\mathrm{BMIM}]\mathrm{Cl}}$ = 0)—lead to:

$$k_{\mathrm{eff}}=k_0\mathrm{e}^{0.74Xc_{\mathrm{MIM},0}} \qquad (3)$$

(Comment: ethanol as a solvent has a negligible influence on k_{eff} since k_0 is not influenced by different ethanol concentrations.)

The strong influence of the salt effect on the rate of the IL-synthesis is shown in Fig. 4 for the minimum amount of solvent needed for single-phase synthesis (20 vol% ethanol) as well as for a relatively high excess of solvent (60 vol%). For both cases, the progress of the measured conversion is

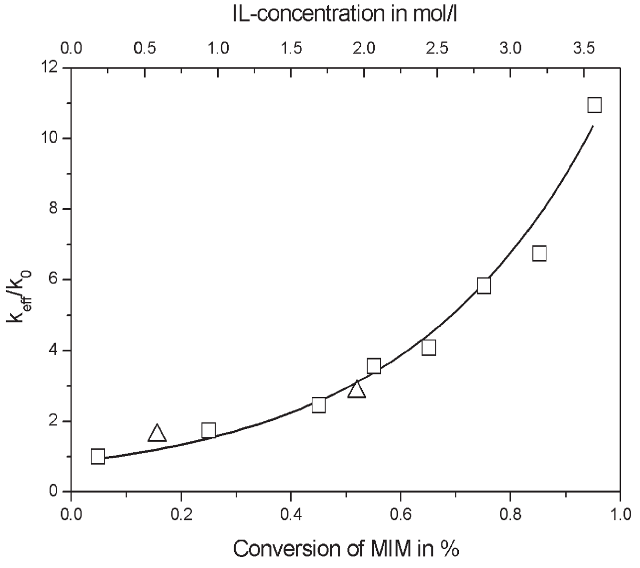

Fig. 3 Progress of effective rate constant k_{eff} normalised to initial rate constant k_0 as a function of MIM-conversion and IL-concentration during single-phase synthesis (rate constant based on slope of $X(t)$: squares; rate constant based on experiments with different initial IL-concentrations: triangles; $c_{\mathrm{MIM},0}$ = 3.75 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu},0}$ = 4.79 mol l^{-1}, 3.55 mol l^{-1} ethanol (20 vol%), T = 66 °C).

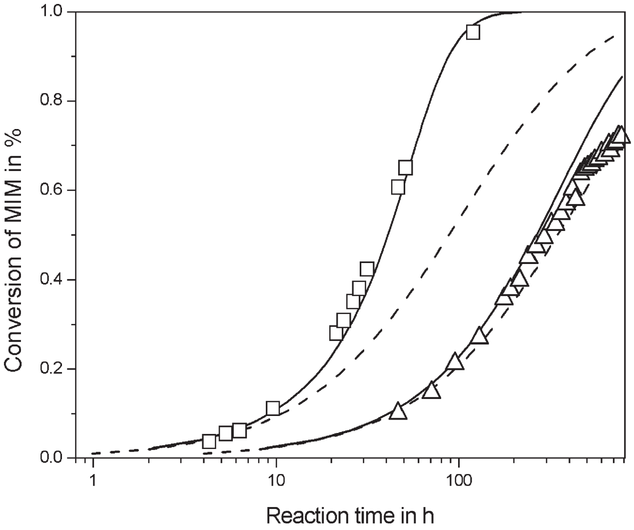

Fig. 4 Conversion of MIM as a function of reaction time during single-phase synthesis with low and high contents of ethanol as solvent: comparison of experimental data and results of calculation taking into account the salt effect (solid line) and neglecting this effect ($k_{\mathrm{eff}} = k_0$; dashed line); squares: experiment with 3.55 mol l^{-1} ethanol (20 vol%), $c_{\mathrm{MIM},0} = 3.8$ mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu},0} = 4.8$ mol l^{-1}, 66 °C, $k_0 = 6 \times 10^{-7}$ l (mol s)$^{-1}$; triangles: experiment with 12.6 mol l^{-1} ethanol (60 vol%), $c_{\mathrm{MIM},0} = 1.24$ mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu},0} = 1.77$ mol l^{-1}, 64 °C, $k_0 = 4 \times 10^{-7}$ l (mol s)$^{-1}$.

compared to the calculation (based on an integration of eqn. (2) and (3)[11,14]). In order to further highlight the influence of the salt effect, the result of a calculation neglecting this effect ($k_{\mathrm{eff}} = k_0$) is included (dashed lines in Fig. 4). Comparison between the experimental and theoretical conversion clearly indicates that the single-phase synthesis can only be modelled if the salt effect is taken into consideration. The salt effect has to be considered above all in the case of a minor content of solvent (20 vol% ethanol).

Kinetics of stirred two-phase [BMIM]Cl-synthesis

In the case of the neat synthesis, two phases are formed for $X > 8\%$, leading to an emulsion of IL–MIM-droplets (passive phase) within the reaction phase if the lab-scale batch reactor is vigorously stirred. In this two-phase system, the salt effect has by nature no influence on the rate (and can also be neglected for the single-phase stage up to $X = 8\%$, Fig. 3). Assuming that the partitioning equilibrium is established according to Nernst's law, the MIM-concentration decreases in the reaction phase compared to the hypothetic case of formation of a pure IL-phase. The Nernst coefficient K, defined as the ratio of the MIM-concentration in the passive phase to the one in the reaction phase, was determined by two methods:

(1) During the synthesis without stirring (see also the following section), the MIM-concentration in both phases was measured. The difficulty with this method is the assumption that the partition equilibrium is always instantaneously established during synthesis, *i.e.* disregarding any influence of mass transfer. Consequently K was determined here based only on the initial phase of the two-phase synthesis ($8\% < X < 40\%$); thereafter ($X > 40\%$), the diffusion of MIM within the enlarged IL-phase has to be taken into account (more and more), leading to an *apparent* increase of the value of the partition coefficient K.

(2) To exclude the influence of diffusion, a mixture of MIM, [BMIM]Cl, and toluene (instead of Cl-Bu) was used as a substitutional system to determine (at least approximately) the partition coefficient: toluene, like Cl-Bu, is insoluble in the IL and completely miscible with MIM, but less polar than Cl-Bu. This is indicated by the so-called $E_{\mathrm{T}}(30)$-value which is an empirical measure for the solvent polarity based on molar transition energy measurements of dyes dissolved in a solvent by its intramolecular charge-transfer absorption bands (toluene: $E_{\mathrm{T}}(30) = 142$ kJ mol^{-1}, 1-chloropropane (which should have a similar polarity as Cl-Bu): $E_{\mathrm{T}}(30) = 156$ kJ mol^{-1}, for comparison H_2O: $E_{\mathrm{T}}(30) = 263$ kJ mol^{-1}).[15] Nevertheless, almost the same K-value of about 2 ($c_{\mathrm{MIM,IL}}/c_{\mathrm{MIM,toluene}}$) is found as during the synthesis.

The reaction kinetics and the conversion with time can be described and calculated by integration[14] of eqn. (4), which is derived, if eqn. (1) is now applied to the two-phase system:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = k_0 \times c_{\mathrm{MIM,rp}} \times c_{\mathrm{Cl\text{-}Bu,rp}} \times \frac{V_{\mathrm{rp}}}{n_{\mathrm{MIM},0}}$$

with

$$\begin{aligned} c_{\mathrm{MIM,rp}} &= \frac{n_{\mathrm{MIM,rp}}}{V_{\mathrm{rp}}} = \frac{n_{\mathrm{MIM,rp}}}{V_{\mathrm{Cl\text{-}Bu}} + V_{\mathrm{MIM,rp}}} \\ c_{\mathrm{Cl\text{-}Bu,rp}} &= \frac{n_{\mathrm{Cl\text{-}Bu,rp}}}{V_{\mathrm{rp}}} = \frac{n_{\mathrm{Cl\text{-}Bu,rp}}}{V_{\mathrm{Cl\text{-}Bu}} + V_{\mathrm{MIM,rp}}} \\ V_i &= \frac{n_i M_i}{\rho_i} \\ n_{\mathrm{MIM,rp}} &= -\frac{KV_{\mathrm{[BMIM]Cl}} + KRV_{\mathrm{MIM},0} + V_{\mathrm{Cl\text{-}Bu}} - RV_{\mathrm{MIM},0}}{(A - AK) \times 2} - \\ &\sqrt{\frac{(KV_{\mathrm{[BMIM]Cl}} + KRV_{\mathrm{MIM},0} + V_{\mathrm{Cl\text{-}Bu}} - RV_{\mathrm{MIM},0})^2}{(A - AK)^2 \times 4} - \frac{V_{\mathrm{Cl\text{-}Bu}} R n_{\mathrm{MIM},0}}{A - AK}} \end{aligned} \tag{4}$$

with

A: ratio of molar mass to density of MIM ($= M_{\mathrm{MIM}}/\rho_{\mathrm{MIM}}$) ($\mathrm{m}^3$ mol^{-1}),

R: dimensionless rest content ($= 1 - X$).

For the neat (two-phase) synthesis, the rate constant is by nature not affected by the salt effect and therefore equivalent to k_0. To solve eqn. (4), the reactant concentrations in the reaction phase, the volumes of the reaction and passive phase, all of which depend on the reaction progress, and the K-value are required. The small contraction of the total volume—max. 10% for $X = 100\%$—was again neglected. The lengthy solution (integrated form of eqn. (4)) is not specified here; details are given elsewhere.[11]

If the rate constant k_0 of the single-phase system is used for the calculation, the best fit is obtained for a K-value of 0.1 (Fig. 5); if the experimentally determined value for K of 2 is used, the best fit is obtained for a higher value of k_0 (factor 2) compared to the single-phase experiment. Considering the complexity of the system, this deviation is still acceptable.

The Arrhenius plot of the rate constant k_0 based on the two-phase experiments, determined from the respective initial rates, is shown in Fig. 6. For comparison, the values based on the

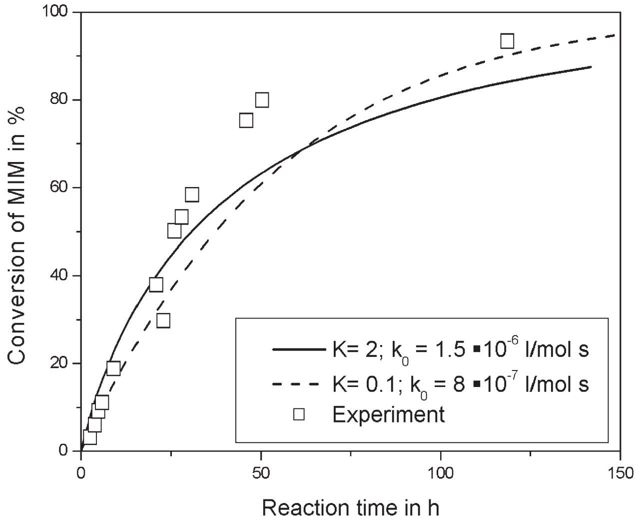

Fig. 5 Stirred two-phase synthesis: comparison of calculated and experimental conversion as a function of time ($c_{\mathrm{MIM},0}$ = 4.2 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu},0}$ = 6.4 mol l^{-1}, 66 °C).

single-phase experiments are also shown. The agreement is quite sufficient, and the activation energies are also similar (single-phase synthesis: 79 kJ mol^{-1}; two-phase: 87 kJ mol^{-1}).

Kinetics of non-stirred two-phase [BMIM]Cl-synthesis

The neat [BMIM]Cl-synthesis becomes cloudy at 8% conversion and an emulsion of IL–MIM droplets in the reaction phase is formed. If the batch reactor is not stirred, separation of the second (passive) IL-rich phase starts immediately, while the upper cloudy phase contains small amounts of IL–MIM droplets settling down into the passive phase, although IL could not be detected by HPLC. The amount of IL in the reaction phase strongly decreases with progress of the reaction and the reaction phase becomes clearer. The complete separation into an IL-free and an IL-rich phase for $X > 8\%$ was verified by titration of the reaction phase after complete phase separation overnight at −16 °C (to eliminate further reaction) and subsequent centrifugation at room temperature: The titration of chloride with $\mathrm{AgNO_3}$ showed no measurable Cl-content.

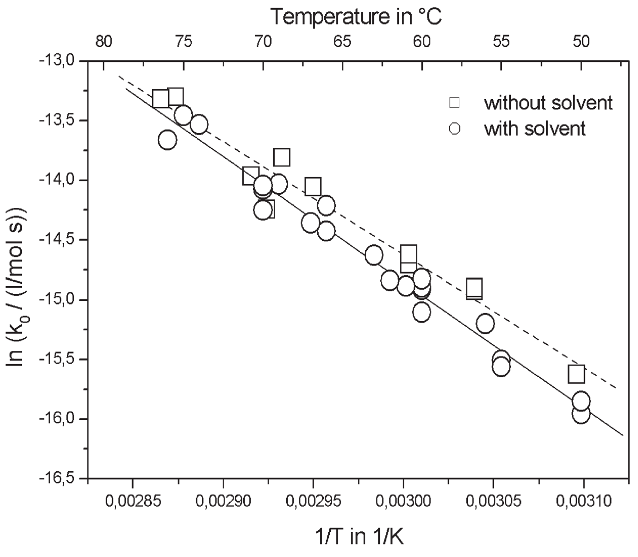

Fig. 6 Arrhenius plot of the rate constant k_0 of [BMIM]Cl synthesis with solvent (single-phase system) and without solvent (neat synthesis with two phases).

For the (non-stirred) two-phase synthesis the amount of MIM rapidly decreases in the reaction phase and increases in the passive phase during the first stage of synthesis up to a conversion of about 50% (Fig. 7, $t < 25$ h). Thereafter ($X > 50\%$), more and more IL is formed and MIM diffuses from the passive phase into the reaction phase by the driving force of the Nernst's partition (Fig. 7, $t > 25$ h).

Initially, the stirred and non-stirred synthesis proceed similarly with respect to the progress of synthesis (Fig. 8). Divergence starts at about 40% conversion (20 h) due to the strong decrease of the amount of MIM in the reaction phase (Fig. 7). Obviously, the effective reaction rate is strongly reduced by the slow MIM-diffusion from the passive to the reaction phase. Therefore, for a technical synthesis, the reactor would have to be stirred to exclude an influence of diffusion on the reaction rate by minimising the diffusion length (small droplets).

An indication of the relatively slow diffusion of MIM in the IL was obtained by an additional exchange experiment with toluene instead of Cl-Bu: toluene was added to a flask initially filled with a mixture of [BMIM]Cl and MIM. Subsequently, the concentration of MIM which diffuses into the toluene-phase was measured; the height of both phases was equivalent to a typical synthesis experiment. The characteristic diffusion time needed is in the order of magnitude of about 10 h (80% approach to equilibrium value).

Comparison of single-phase and stirred two-phase synthesis

The comparison of single-phase synthesis (minimum amount of solvent) and stirred neat synthesis at 75 °C (Fig. 9) indicates that in both cases the time needed for a given conversion is about the same; this result was also obtained for other temperatures (*e.g.* 66 °C).[11] This surprising effect can be explained by the coincidence of two circumstances:

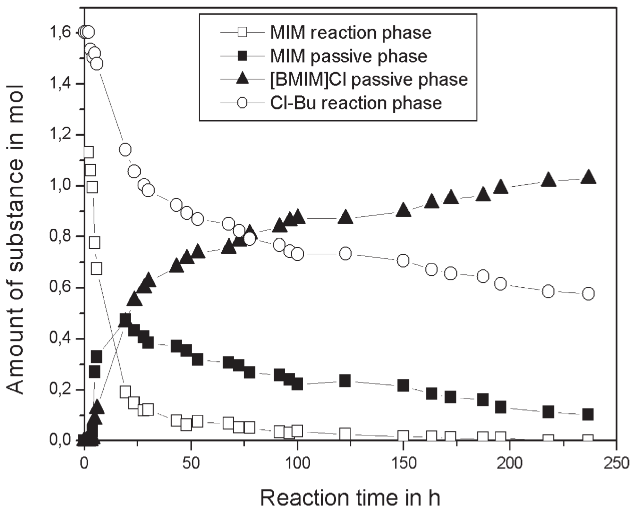

Fig. 7 Progress of non-stirred two-phase synthesis of [BMIM]Cl ($c_{\mathrm{MIM},0}$ = 4.11 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu},0}$ = 6.45 mol l^{-1}, 70 °C; the smallest amount of IL in the reaction phase during the initial single-phase ($t < 10$ h) is omitted).

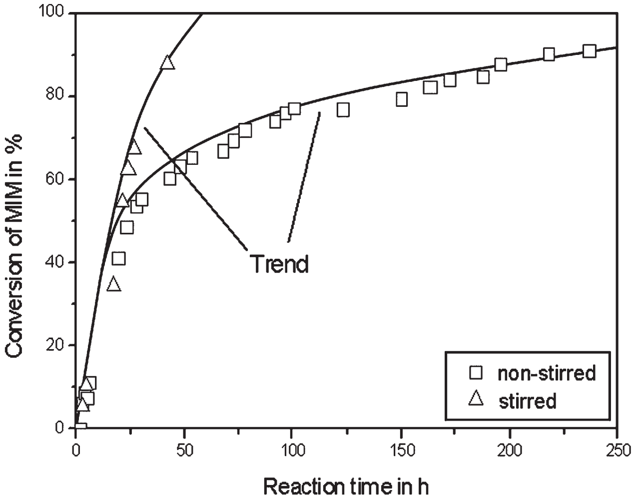

Fig. 8 Comparison of stirred and non-stirred two-phase synthesis ($c_{\mathrm{MIM,0}}$ = 4.1 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu,0}}$ = 6.5 mol l^{-1}, 70 °C).

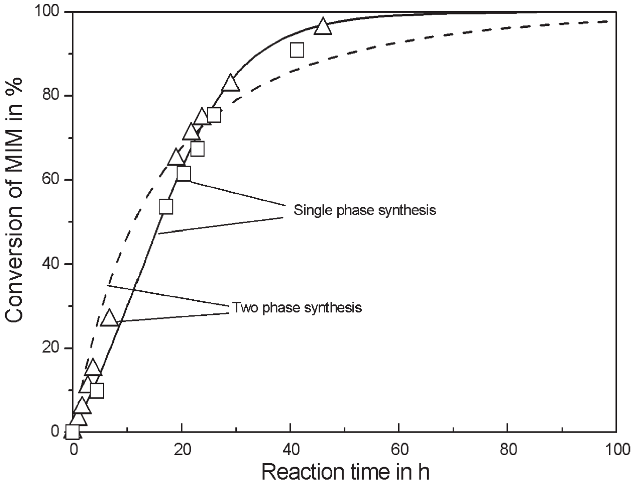

Fig. 9 Single-phase and stirred two-phase synthesis: comparison of calculation and experiment for 75 °C (single phase, with salt effect: experiment: squares, model: solid line; two-phase with partition coefficient: experiment: triangles, model: dashed line; single-phase: $c_{\mathrm{MIM,0}}$ = 3.29 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu,0}}$ = 4.56 mol l^{-1}, 3.29 mol l^{-1} ethanol (20 vol%); two-phase: $c_{\mathrm{MIM,0}}$ = 4.47 mol l^{-1}, $c_{\mathrm{Cl\text{-}Bu,0}}$ = 6.18 mol l^{-1}).

(1) The salt effect increases the effective rate constant of the single-phase synthesis (Fig. 3), but not of the neat synthesis, where the IL is separated by the formation of a second phase. Therefore, this circumstance favours single-phase synthesis.

(2) During neat synthesis, the reactant concentrations (above all of Cl-Bu) remain high and the volume of the reaction phase decreases. During single-phase synthesis, the reactant concentrations decrease with proceeding conversion and the volume of the reaction phase (total volume) is constant. In summary, this circumstance favours the neat synthesis (see example below).

The following rough estimation may elucidate this complex interplay; for simplification, the partition of MIM in both phases for the neat synthesis is neglected: For the single-phase synthesis, the rate of IL-formation is given by $0.64 \times k_{\mathrm{eff}} \times c_{\mathrm{MIM}} \times c_{\mathrm{Cl\text{-}Bu}} \times V_{\mathrm{rf}} \approx 0.64 \times 3k_0 \times (1 - X)^2 \times c_{\mathrm{MIM,0}} \times c_{\mathrm{Cl\text{-}Bu,0}} \times V_0$, whereby the factor 0.64 takes into account the dilution with ethanol (20 vol%) and the factor 3 the salt effect (k_{eff} (X = 50%) = $3k_0$, see Fig. 3). For the neat synthesis, the rate is given by $k_0 \times c_{\mathrm{MIM}} \times c_{\mathrm{Cl\text{-}Bu}} \times V_{\mathrm{rp}} \approx k_0 \times c_{\mathrm{MIM,0}} \times c_{\mathrm{Cl\text{-}Bu,0}} \times (1 - X) \times V_0$. So for a conversion of *e.g.* 50%, the estimated rates for the single-phase and neat synthesis are almost the same: $0.48(k_0 \times c_{\mathrm{MIM,0}} \times c_{\mathrm{Cl\text{-}Bu,0}} \times V_0)$ and $0.50(k_0 \times c_{\mathrm{MIM,0}} \times c_{\mathrm{Cl\text{-}Bu,0}} \times V_0)$, respectively.

For the given reaction conditions, these two circumstances obviously compensate each other, and thus the effective conversion rate is almost equal (Fig. 9). As a result, neat synthesis is advantageous for industrial IL-production, as the subsequent separation of a solvent (*e.g.* ethanol) is not required.

One additional aspect—neglected in the above estimation—should be discussed. In the case of two-phase synthesis, MIM is also dissolved in the passive IL-phase. With increasing conversion and amount of IL, this effect slows down the rate compared to the case where only pure IL forms the passive phase. Consequently, the rate of the two-phase synthesis is lower compared to single-phase synthesis for a conversion of more than about 70%, see Fig. 9.

Continuous two-phase synthesis process

Finally, the neat synthesis was also conducted at 75 °C in a small continuous tubular steel reactor (length: 6 m; diameter: 3 mm) at a residence time of 70 h. The experimental results clearly highlight the feasibility of continuous IL-production. (Problems were only caused by the very corrosive properties of the solution, above all in combination with unavoidable traces of water.) The conversion of MIM was 98 ± 1% which is equivalent to the value reached in the stirred batch reactor at the same reaction time (see Fig. 9). So, mixing (dispersion) in the tubular reactor is obviously sufficient to suppress diffusional resistances.

The scale-up of continuous IL-production is therefore easily possible, *e.g.* for a production rate of 10 kg IL per day a simple tubular reactor with a length of 10 m and a diameter of 5 cm (residence time 70 h) would be needed.

Tracking of synthesis by an electrical conductivity method

In general, tracking of the reaction progress is difficult, since ILs are non-volatile. HPLC—as used in this study—is time consuming and extensive with respect to developing an adequate method. So, electrical conductivity measurements in the single-phase system were also performed using an in-house Teflon conductivity sensor which is stable under the reaction conditions. By this means the reaction progress could easily be monitored *in situ* up to a conversion of about 80% (almost linear increase of the conductivity with conversion[11]). For a higher conversion and higher ion concentrations, respectively, the resolution of the sensor is insufficient, but off-line monitoring is still possible by a defined dilution of samples with ethanol.

Conclusions and outlook

[BMIM]Cl synthesis follows a kinetic 2nd order, *i.e.* 1st order with respect to both reactants. For single-phase IL-synthesis with ethanol as a solvent (>20 vol%), the effective reaction rate constant increases with the progress of the synthesis (salt effect). Solvent-free synthesis leads to a two-phase system for a conversion >8% with the partition of MIM in both phases.

The agreement of the measured and calculated reaction progress in the single- as well as in the two-phase system is sufficient. Modelling was based on the experimentally determined thermodynamic and kinetic data.

The rates of IL-formation for the (stirred) two-phase and the single phase synthesis (20 vol% ethanol) are almost the same, which is the result of the counterbalance of the salt effect (favouring single-phase synthesis) and the higher reactant concentration (favouring neat synthesis). As a consequence, neat synthesis is advantageous for industrial production, since the subsequent separation of a solvent is not required.

With respect to a continuous synthesis, the (neat) synthesis was also conducted successfully in a tubular reactor. The residence time was equivalent to the reaction time required in the batch process.

The reaction progress can be monitored either by time-consuming HPLC-analysis or, alternatively, by *in situ* electrical conductivity measurements.

Further kinetic investigations are currently performed on the synthesis of a second IL, 1-ethyl-3-methylimidazolium ethylsulfate,[11] thereby combining conductivity measurements and a continuous tubular tap-reactor to monitor the progress of the synthesis. Contrary to [BMIM]Cl, the synthesis of [EMIM]EtSO$_4$ is fast (characteristic reaction time of less than 1 min compared to more than 50 h for [BMIM]Cl) and thermal effects have to considered, *i.e.* an efficient cooling of the tubular reactor is essential.

Experimental

Chemicals

The starting materials were purchased from BASF (1-methylimidazol) and Fluka (1-chlorobutane), respectively.

HPLC solvents for analysis (methanol and water) were purchased from Fisher Scientific and for the ion pair chromatography sodium 1-hexylsulfonate salt was used from Acros.

Analytical methods

HPLC: the chromatographic system included a Varian Pro Star 210 solvent delivery system and Pro Star UV/VIS 320 absorbance detector. The column was an Omnisper C18 (4,6 mm i.d. × 250 mm, Varian). A methanol–water (1 : 1) mixture with 1×10^{-3} mol l^{-1} ion pair reagent was used as a solvent.

Conductivity measurements were carried out with two stainless steel electrodes, a Teflon ferrule sensor (cell constant $C_{\text{cell}} = 0.98$, as determined by aqueous KCl standard solution).

Discontinuous preparation of [BMIM]Cl

Stirred batch reactor: in a three-necked, 500 ml round-bottomed flask equipped with reflux condenser, KPG stirrer, thermometer and sample fountain 1-chlorobutane was heated up to reaction temperature either with or without solvent (20 vol% ethanol). At the desired temperature, 1-methylimidazol of the same temperature was added. The reaction mixture (typically 200 ml) was stirred up to 200 h and samples were taken with a syringe and analysed by HPLC (retention times: MIM = 7.9 min, [BMIM]Cl = 12.3 min).

Non-stirred batch reactor: the two reactants were heated up separately to the desired temperature and then combined and stirred for 5 min. Thereafter, mixing was stopped and reaction mixture was kept at a constant temperature up to a reaction time of 250 h. Samples were taken from both phases using a syringe.

Triangular phase diagram

The triangular phase diagram was determined by adding one component (for example Cl-Bu) dropwise to a given mixture of the other two components (for example MIM and [BMIM]Cl) until at 70 °C a second phase is observed.

Partition coefficient

Non-stirred batch reactor: For the determination of the Nernst partition coefficient, the MIM-concentration in both phases was analysed by HPLC.

Model system: a mixture of toluene, [BMIM]Cl, and MIM was stirred at a given temperature in a Schlenk tube for 10 minutes. After phase separation (10 minutes) both phases were analysed by HPLC.

Continuous preparation of [BMIM]Cl

Continuous [BMIM]Cl synthesis was carried out in a heated stainless steel tubular reactor (length: 6 m, diameter: 3 mm). The mixture of the reactants was pumped by a Varian 210 HPLC pump with a flow rate of 0.6 ml h^{-1}. The reaction temperature was set at 75 °C.

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11 - 13 December 2005

The RSC's Environment, Sustainability and Energy Forum (ESEF) is pleased to announce an international conference on ***Catalysis and Biocatalysis in Green Chemistry*** to be held in Cambridge in December 2005.

This conference is intended to bring together the various distinct catalysis communities, foster new collaborations and to stimulate discussion of current trends in the field of green chemistry. It represents a new approach to tackling key research issues in this important subject area.

Green catalysis holds the key for significant chemical process optimisations: new catalytic transformations, elimination or reduction of hazardous process solvents, new reactor designs and novel catalytic materials (including biocatalysts) that can selectively transform raw materials to products achieving higher yields and reducing formation of by-products. Advances in catalysis and biocatalysis will therefore play a pivotal role in reducing the environmental footprint of chemical processes while also increasing commercial competitiveness through increased efficiency.

Topics include:

- new catalytic transformations
- the exploitation of renewable feedstocks
- biocatalysis as an alternative greener route for production of chemicals
- design and synthesis of new and more efficient catalysts for environmentally benign processes
- new technologies: simultaneous conversion-separation processes: scaled-down process design

Invited speakers will include:

Dr Paul Anastas, *Green Chemistry Institute, ACS, USA*
Professor Alfons Baiker, *ETH, Switzerland*
Professor John Frost, *Michigan State University, USA*
Professor Klavs Jensen, *MIT, USA*
Professor Shu Kobayashi, *University of Tokyo, Japan*
Dr Isao Noda, *The Proctor and Gamble Company, USA*
Dr John Pierce, *Dupont, USA*
Professor Roger Sheldon, *Delft University of Technology, The Netherlands*

This meeting is supported by the journal *Green Chemistry* and sponsored by the Green Chemistry Institute of the ACS, the IChemE and the EPSRC.

The deadline for oral abstracts is 29th April.

For more information on how to submit an abstract to this conference, details of the programme and sponsorship opportunities, please visit the RSC Conferences website: **www.rsc.org/conferences.**

Alternatively tel **+44 (0) 1223 432254** or email **conferences@rsc.org**

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