Green Chemistry

Cutting-edge research for a greener sustainable future

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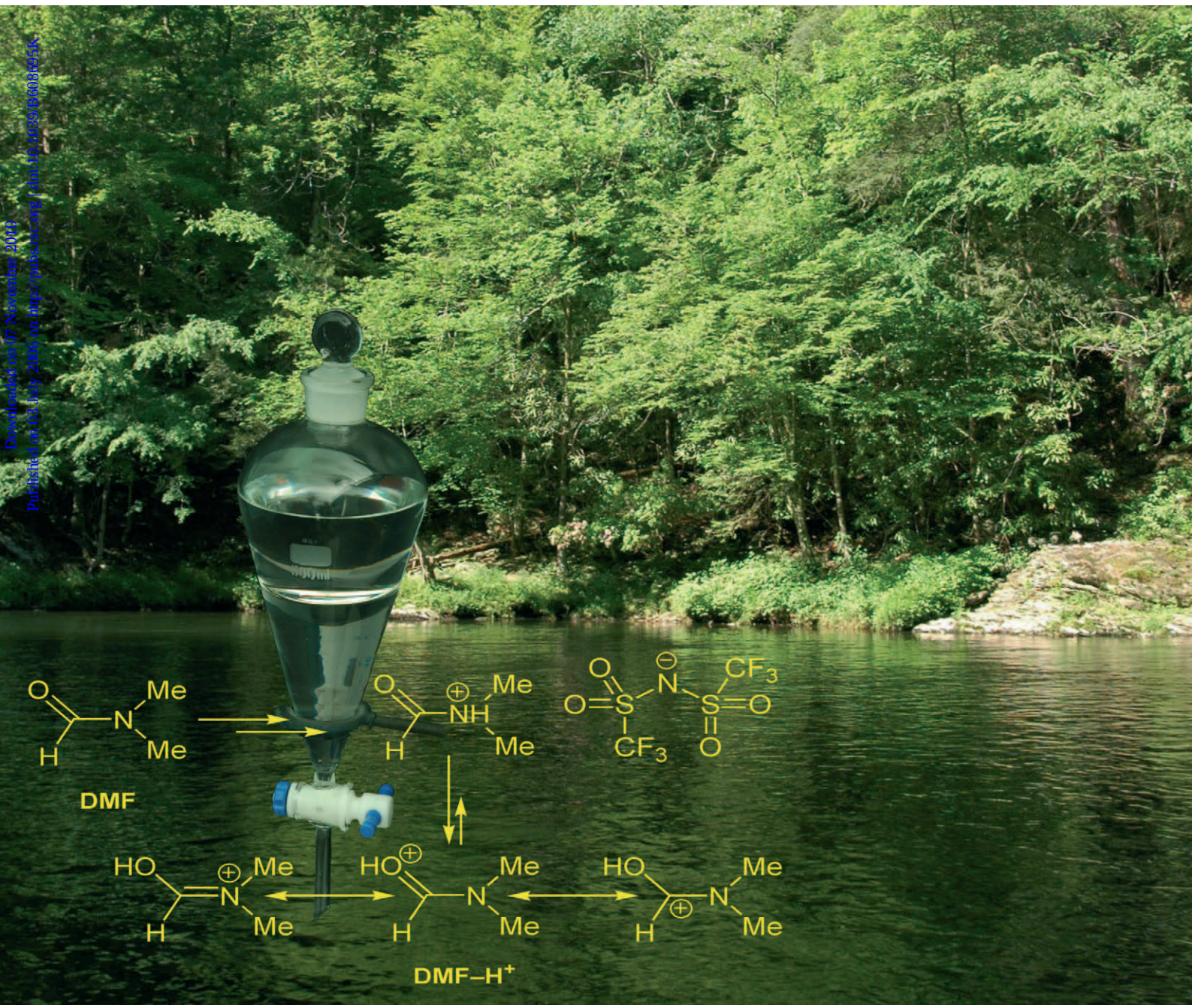
Volume 8 | Number 7 | July 2006 | Pages 585–664



ISSN 1463-9262

Adam *et al.*
Chemical reactivity in ionic liquids

Huang *et al.*
Brønsted acidic ionic liquids derived from DMF

Shimizu *et al.*
Mannich type reactions in water

Stolte *et al.*
Anion effects on the cytotoxicity of ionic liquids

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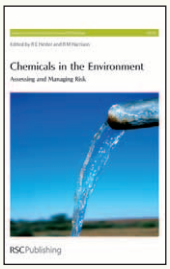

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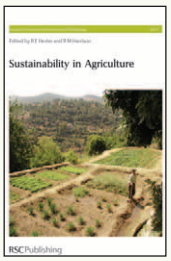

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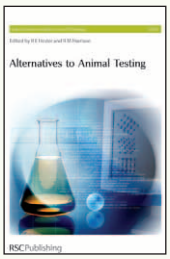

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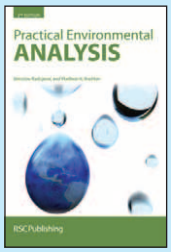

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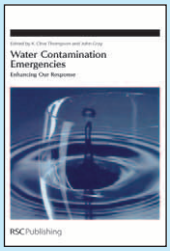

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New protic ionic liquids based on amide moieties have been developed as novel proton-conducting media for potential applications in fuel cells. Image reproduced by permission of Sheng Dai from *Green Chem.*, 2006, **8**(7), 599.

CHEMICAL TECHNOLOGY

T25

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

Chemical Technology

July 2006/Volume 3/Issue 7

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HIGHLIGHT

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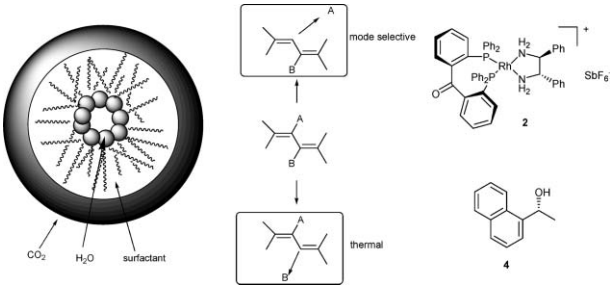
Highlights

Markus Hölscher reviews some of the recent literature in green chemistry.



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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.

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

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COMMUNICATIONS

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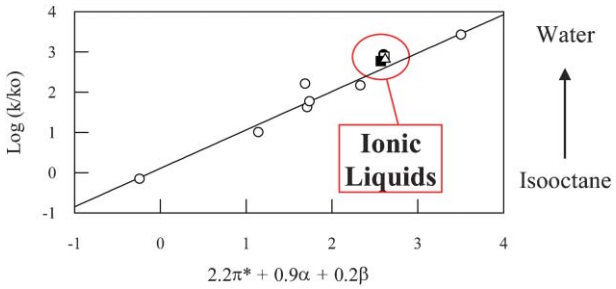
Chemical reactivity in ionic liquids: Nitroso group transfer from *N*-nitrososulfonamide

Claudia Adam, Luis García-Río,* Ana Godoy and J. Ramón Leis

Nitroso group transfer in ionic liquids exhibits good correlation with the polarity parameters of the ionic liquid, showing that the amine nucleophilicity in not increased on going from water to the ionic liquid.



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Brønsted acidic room temperature ionic liquids derived from *N*,*N*-dimethylformamide and similar protophilic amides

Jing-Fang Huang, Gary A. Baker, Huimin Luo, Kunlun Hong, Qing-Feng Li, Niels J. Bjerrum and Sheng Dai*

We herein describe a convenient and efficient one-pot route to a new family of cost-effective, highly proton conductive room temperature ionic liquids based on *N*,*N*-dimethylformamide.

PAPERS

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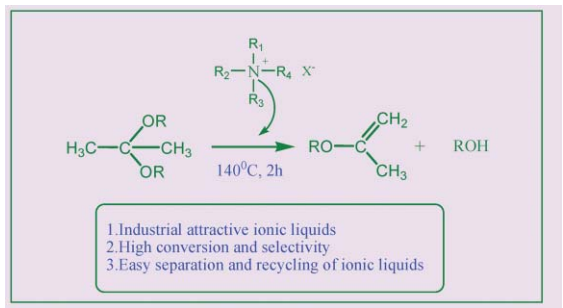
Preparation of simple ammonium ionic liquids and their application in the cracking of dialkoxypropanes

Congmin Wang, Liping Guo, Haoran Li,* Yong Wang, Jianyang Weng and Lianhai Wu

A series of simple ammonium ionic liquids are prepared and used as acidic catalysts for the synthesis of alkoxypropenes. High conversion and selectivity are obtained in sulfate ionic liquids without the use of inorganic acid catalysts and volatile organic solvents.



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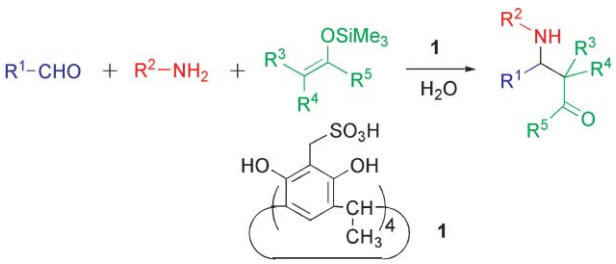
Mannich-type reactions in water using anionic water-soluble calixarenes as recoverable and reusable catalysts

Shoichi Shimizu,* Naoyuki Shimada and Yasuyuki Sasaki

The water-soluble calix[4]resorcinarene sulfonic acid can be recovered as an aqueous solution and recycled.



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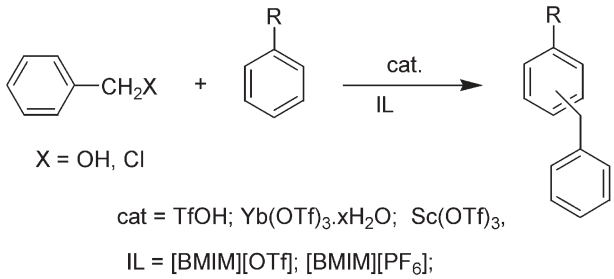

Facile benzylation of aromatics in ionic liquid solvents promoted by TfOH, $Sc(OTf)_3$, and $Yb(OTf)_3 \cdot xH_2O$; New life for a classic transformation

Viorel D. Sarca and Kenneth K. Laali*

Benzylation of arenes can be carried out efficiently in imidazolium ionic liquids employing $PhCH_2OH$ and $PhCH_2Cl$ as benzylating agents and TfOH, $Yb(OTf)_3$ or $Sc(OTf)_3$ as promoters.

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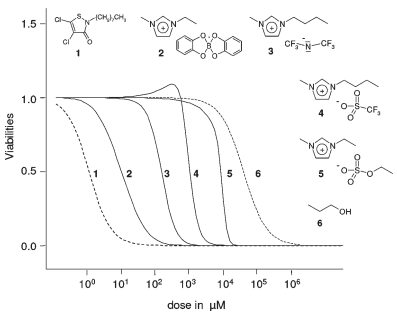

Anion effects on the cytotoxicity of ionic liquids

Stefan Stolte, Jürgen Arning, Ulrike Bottin-Weber, Marianne Matzke, Frauke Stock, Karen Thiele, Marc Uerdingen, Urs Welz-Biermann, Bernd Jastorff and Johannes Ranke*

As most recent investigations are predominantly focusing on the cation moieties, in this study we elucidate, whether the anion species commonly used in ionic liquids exhibit intrinsic cytotoxic effects and if these effects can be rationalised by thinking in terms of structure–activity relationships.

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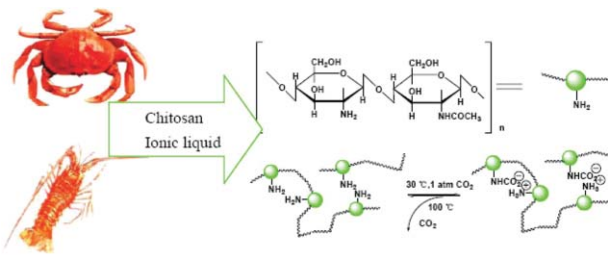

Chitin and chitosan dissolved in ionic liquids as reversible sorbents of CO_2

Haibo Xie, Suobo Zhang* and Shenghai Li

A novel dissolving process for chitin and chitosan has been developed by using the ionic liquid 1-butyl-3-methyl-imidazolium chloride ([Bmim]Cl) as solvent, and a novel application of chitin and chitosan as substitutes for amino-functionalized synthetic polymers for capturing and releasing CO_2 has also been exploited based on this processing strategy.

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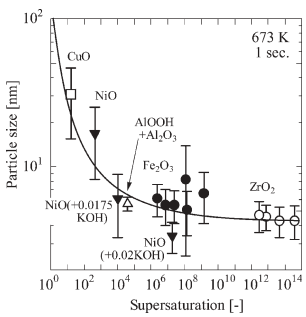

Size-controlled synthesis of metal oxide nanoparticles with a flow-through supercritical water method

Kiwamu Sue,* Muneyuki Suzuki, Kunio Arai, Tomotsugu Ohashi, Haruo Ura, Keitaro Matsui, Yukiya Hakuta, Hiromichi Hayashi, Masaru Watanabe and Toshihiko Hiaki

Metal oxide nanoparticles were synthesized with a flow-through supercritical water method. Effect of experimental condition on particle size was analyzed on the basis of supersaturation.

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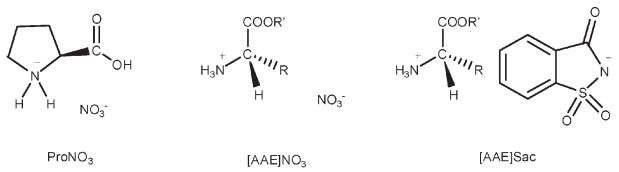
Preparation, characterization and application of amino acid-based green ionic liquids

Guo-hong Tao, Ling He, Wei-shan Liu, Lin Xu, Wei Xiong, Tao Wang and Yuan Kou*

A family of novel ionic liquids with amino acids and their derivatives as cations and environmentally benign materials as anions have been synthesized using easy preparation techniques.



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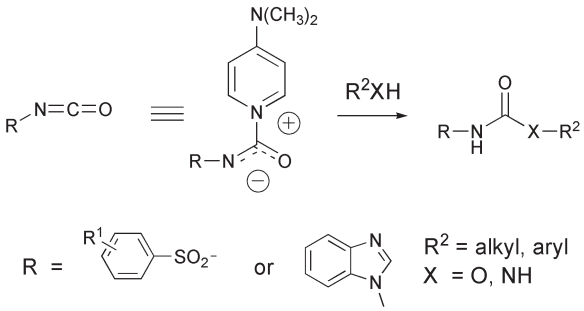
4-Dimethylaminopyridinium carbamoylides as stable and non-hazardous substitutes of arylsulfonyl and heteroaryl isocyanates

Franciszek Sączewski,* Anita Kornicka and Zdzisław Brzozowski

Dimethylaminopyridinium carbamoylides (**3a–d** and **25**) have been designed as new, safer and non-hazardous substitutes of arylsulfonyl isocyanates and the previously unreported benzimidazol-1-yl isocyanate.



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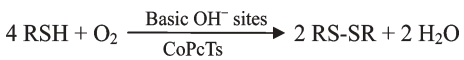
Catalytic oxidation of mercaptans by bifunctional catalysts composed of cobalt phthalocyanine supported on Mg–Al hydrotalcite-derived solid bases: effects of basicity

Haichao Liu* and Enze Min

Mg–Al mixed oxide solid bases derived from Mg–Al hydrotalcites with cobalt phthalocyanine tetrasulfonate are efficient for mercaptan oxidation, instead of caustic soda, and their surface OH^- rather than O^{2-} sites and medium base strength are required for achieving high turnovers.



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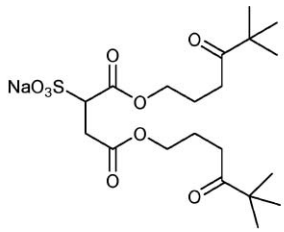
Highlights

DOI: 10.1039/b607669f

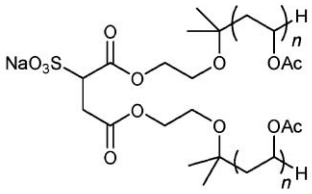
Markus Hölscher reviews some of the recent literature in green chemistry.

Novel CO_2-philes for stabilized H_2O/CO_2-microemulsions

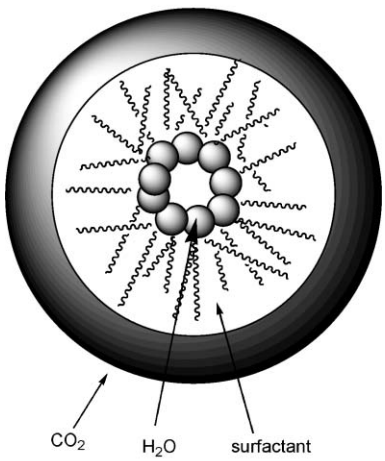
The environmental advantages of compressed and/or supercritical CO_2 as a solvent in chemical production rely mainly on the fact that it can be separated from the dissolved matter very easily by simply reducing the pressure—regenerating gaseous CO_2 which subsequently is repressurized for further usage. Furthermore CO_2 is cheap, nontoxic, nonflammable and abundant, suggesting it to be *the* ideal solvent for sustainable production and handling of chemical products. However, with a few special exceptions its solvent properties are, by far, not competitive for the vast majority of applications. The problem has been addressed by developing fluorinated surfactants, which together with CO_2 generate emulsions with acceptable solvent properties. However, by introducing fluorine into the systems the environmental benefits immediately vanish. Pure hydrocarbon surfactants do not solve the problem, but oxygenated hydrocarbons seem to be promising candidates for the generation of CO_2/H_2O emulsions with significant power for dissolving common chemical compounds, pharmaceuticals, catalysts *etc.* The surfactant AO-Vac is one of the promising candidates for the stabilization of H_2O/CO_2 phases and very recently Eastoe *et al.* from the University of Bristol investigated, by means of high-pressure small-angle neutron scattering (HP-SANS), the structural parameters of H_2O/CO_2 microemulsions in the presence of AO-Vac and the model complex AOK.[1] While a set of standard hydrocarbon surfactants did not stabilize nanodroplets of H_2O in CO_2, both AOK and AO-Vac showed SANS signals which by careful interpretation of the analytic data suggested the existence of H_2O nanodroplets surrounded by a surfactant shell embedded in CO_2. The droplet radii ranging from the midpoint of the H_2O core through the surfactant area to the beginning of the CO_2 phase varied between 8 and 26 Å, suggesting droplet sizes and properties to be tunable for achieving the desired properties.



AOK



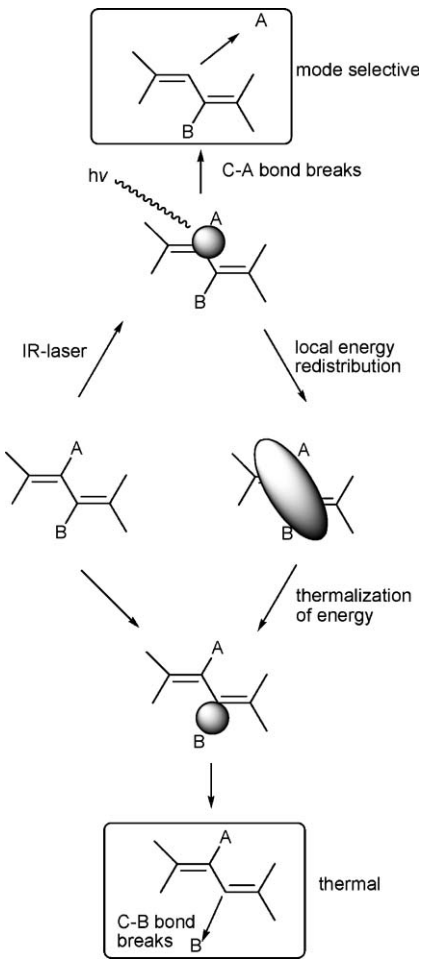
AO-Vac



schematic representation of the microemulsion

IR-induced mode selective chemistry in reactions at surfaces

If a single chemical bond of a molecule could be energized selectively giving rise to bond breakage, *i.e.* by means of specifically addressable radiative energy input, other chemical pathways for reactions might be opened, which differ from the dominant thermal pathway. Theoretically a variety of novel transformations should be the result. Ideally multistep chemical transformations could be made more efficient by reducing the required amounts of steps. Though being a very elegant and often tried idea, molecules have by and large not cooperated so far. The main reason is the fast redistribution of vibrational energy to other lower frequency modes, de-exciting the mode that was excited in the initial energy uptake. As a result the thermal pathway again is the favored reaction pathway.



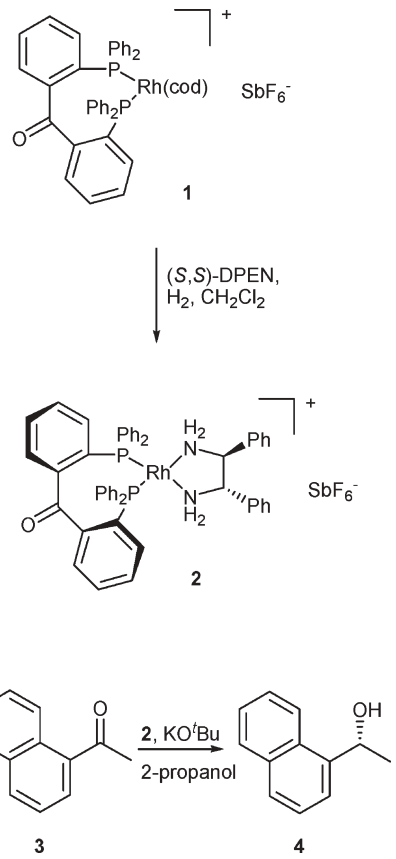
Cohen and coworkers from the university of Minnesota very recently found evidence that mode selective chemistry is possible under certain conditions.[2] The

Si(111)-surface was chosen as appropriate basis for the creation of an adsorption layer of a mixture of H and D atoms (15 : 85). Subsequently the surface was irradiated with a free-electron laser tuned to the 4.8 μm Si–H stretching mode. Surprisingly almost all desorbed atoms were H_2, with less than 5% of desorbing molecules were HD or D_2. A local heating mechanism could be ruled out as the outcome of such a reaction scenario would be a statistical mixture (2% H_2, 26% HD, 72% D_2). The mechanism is unclear at the moment, however IR-mode selective chemistry in a multi-atom system is clearly possible.

Achiral metal complex and chiral amine yield asymmetric catalysts for transfer hydrogenation

State of the art asymmetric catalysis mainly relies on the application of enantiopure catalysts to perform highly enantioselective reactions. However, the synthesis of a chiral catalyst can be tedious due to problems associated with the synthesis and purification of the chiral ligand, by which the chirality usually is introduced into the metal complex. An alternative is the usage of achiral ligands and chiral activator molecules that are either easily available from the chiral pool or can be made more easily than the chiral ligand. Mikami *et al.* from the Tokyo Institute of Technology very recently showed that atropisomeric ligands which are based on the BINAP core can be replaced by the achiral benzophenone core, when chirality is introduced subsequently by a chiral activator molecule.[3] The authors first synthesized achiral complex **1** by simply reacting the appropriate 2,2′-bis-(diphenylphosphino)benzophenone with a cationic rhodium complex.

Subsequently **1** was treated with (*S*,*S*)-diphenylethylenediamine [(*S*,*S*)-DPEN], which resulted in the formation of diasteromerically pure **2**. The catalytic performance of **2** was checked in transfer hydrogenations of various ketones and also it was compared with the performance of "classic" (*R*)-BINAP based catalysts. Interestingly it was found for a number of substrates that conversions no less than 95% are achieved while enantioselectivities can be 99%. In the case of **3**, conversion to alcohol **4** was quantitative and the *ee*-value amounted to 99%.



Tamiflu supply problem solved by two new synthesis routes

The emergence of avian virus H5N1 has caused worldwide concerns about a potential pandemic flu wave as the virus can infect humans. The development of a suitable vaccine is one of the various steps taken to increase worldwide safety; another one is the supply of the orally active anti-influenza drug oseltamivir phosphate 1 (Tamiflu) because it inhibits neuramidase. This enzyme is necessary for spreading the virus from infected cells. However, the current industrial process used by Roche for the synthesis of Tamiflu relies on (−)-shikimic acid or (−)-quinic acid as starting materials which are expensive and of limited availability. Furthermore the synthesis involves some steps with potentially hazardous and explosive azide-containing intermediates. Stimulated by these drawbacks, the groups of Corey[4] and Shibasaki[5] have independently designed two new routes to Tamiflu, which use starting materials that are more easily available and much cheaper. Shibasaki's group has applied for a patent in contrast to Corey *et al.* who simply made their results available to the public. Meanwhile, Roche has made significant efforts to increase Tamiflu production using the conventional way by asking more than 15 contractors to help expand the production of the two key intermediates of the Roche process. As a result, two new academically derived alternative syntheses are available, while production within the current protocol is increased: from a general viewpoint it seems that the Tamiflu supply problem is solved.

Reduction of poverty is inevitable for global sustainablity

A short definition of sustainable development could be as follows: economic growth that is not harmful but fruitful for the environment, of course including the people living in this environment. Poverty is a hindrance in accomplishing this goal because poor people will focus on appeasing hunger and thus ignore environmental restrictions, rather than concentrate on sustainable development. As a result investing in poverty reduction is necessary to establish sustainable development, while investing in the environment reduces poverty. Jeffrey D. Sachs and Walter V. Reid from Columbia University and Stanford University, respectively, have summarized the latest reports and advice by the United Nations Millenium Project and the Milennium Ecosystem Assessment very recently.[6] Both reports emphasize that the current behaviour of rich and poor countries is not sustainable in general. Also, the two reports come to very similar conclusions of how to improve current strategies for poverty reduction. Firstly, some of the central recommendations include the establishment of a Millenium Ecosystem Fund by the rich donor countries to supply poor countries with the necessary capital for incorporation of strategies for environmental sustainability into national development plans. Secondly, the United Nations are advised to establish a regular cycle of global assessment to

monitor in 4 to 5 year periods the changes induced in poverty development. Thirdly, the world scientific community is requested to define interdisciplinary strategies for sustainable development research and thus help to direct governmental decisions towards these challenges.

References

1 J. Eastoe, S. Gold, S. Rogers, P. Wyatt, D. C. Steytler, A. Gurgel, R. K. Heenan, X. Fan, E. J. Beckman and R. M. Enick, *Angew. Chem.*, 2006, **118**, 3757–3759.

2 Z. Liu, L. C. Feldman, N. H. Tolk, Z. Zhang and P. I. Cohen, *Science*, 2006, **312**, 1024–1026.

3 K. Mikami, K. Wakabayashi, Y. Yusa and K. Aikawa, *Chem. Commun.*, 2006, 2365–2367.

4 Y.-Y. Yeung, S. Hong and E. J. Corey, *J. Am. Chem. Soc.*, 2006, **128**, 6310–6311.

5 Y. Fukuta, T. Mita, N. Fukuda, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 6312–6313.

6 J. D. Sachs and W. V. Reid, *Science*, 2006, **312**, 1002.

Chemical reactivity in ionic liquids: Nitroso group transfer from *N*-nitrososulfonamide

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Received 27th February 2006, Accepted 22nd May 2006
First published as an Advance Article on the web 2nd June 2006
DOI: 10.1039/b602902g

Nitroso group transfer in ionic liquids exhibits good correlation with the polarity parameters of the ionic liquid, showing that the amine nucleophilicity in not increased on going from water to the ionic liquid.

Ionic liquids (ILs) are attracting increasing attention from chemists and technologists on account of their usefulness as solvents for various processes including catalytic reactions.[1] The interest has partly arisen in the search for "green" industrial solvents. ILs have been advocated as "green solvents" on the grounds of their negligible vapour pressure.[2,3] Many chemists, however, have also realized that ILs possess some unique properties as solvents. Their ease of preparation and structural modification with a view to modulating their physical properties have turned them into a flexible alternative to molecular organic solvents. Although they have proved excellent media for catalytic processes including Friedel–Crafts,[4] alcohol and phenol oxidation,[5,6] Michael addition,[7] fluorination,[8] and enzymatic reactions,[9] in addition to Heck arylation of electron-rich olefins by aryl halides[10] and electrophilic nitration of aromatics,[11] few studies on chemical reactivity in these media have been reported.

Rather, recent research on ILs has focussed on their effects on chemical processes and the potential relationship of such effects to other measurable solvent properties. Thus, Welton and coworkers determined chloride, bromide and iodide nucleophilicity in the reaction of methyl-*p*-nitrobenzenesulfonate in various ILs.[12,13] They found ILs to reduce rather than enhance halide nucleophilicity relative to molecular solvents. The effect of ILs on nucleophilicity can be ascribed to chloride ion being stabilized through hydrogen bonding to the cation in the IL. Halide ions are known to form strong hydrogen bonds[14] with $[bmim]^+$ and, to a lesser extent, $[bm_2im]^+$; on the other hand, [bmpy] cannot be expected to act as a hydrogen bond donor. Changing the anion in an IL has been found to alter the Kamlet–Taft bond acceptor parameter, β.[15] With chloride as the nucleophile, anion and cation effects are similar in magnitude; with bromide and iodide, however, changing the anion in an IL has a more marked effect than replacing the cation. Chiappe and Pieraccini[16] obtained similar results for the reactions of Br_3^- and ICl_2^- with various alkenes and alkynes in ILs. They found the rates of both reactions to increase from 1,2-dichloroethane to the ILs. Available evidence suggests that, while the hydrogen bonding ability of the imidazolium cation is probably the main factor increasing the rate of addition of ICl_2^- to double and triple bonds, this property has no effect on the electrophilic addition of Br_3^- to alkenes and alkynes. Fulfillment of the Hughes–Ingold rules was checked in a study of amine nucleophilicity in both ILs and molecular solvents.[17] All amines studied were found to be more nucleophilic in the ILs than they were in dichloromethane, acetonitrile and water.

In this work, we studied the nitroso group transfer from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) to secondary amines (Scheme 1) in several ILs in order to examine the use of the Kamlet–Taft solvent parameters with a view to estimating chemical reactivity in various media. The amines used [*viz.* morpholine (MOR), *N*-methylpiperazine (MePIP) and pyrrolidine (PYR)], were subject to similar steric hindrance and spanned a wide basicity range (*viz.* pK_a values from 8.36 for MOR to 11.27 for PYR in water).

Kinetic experiments were conducted as described elsewhere,[18] using λ = 390 nm, T = 25.0 °C and MNTS in understoichiometric amounts relative to the amine. All solutions were prepared in the corresponding IL. The moisture content of the amines was minimized by desiccation with CaH_2 and subsequent collection onto a molecular sieve. The IL was prepared in our laboratory, following previously reported procedures[19] and also obtained from Solvent Innovation; the rate constants obtained in the commercially available liquid were always consistent with those determined in the liquid prepared in our laboratory. Absorbance–time data pairs fitted the first-order integral equation well and the pseudo first-order constant values obtained were reproducible to within ±3%.

As can be seen from Fig. 1, k_{obs} was always linearly related to the amine concentration. The slopes of the lines were used to obtain the bimolecular rate constants, k. The observed linear relationship between k_{obs} and the amine concentration is consistent with the results obtained in most molecular solvents.[20]

The reactivity sequence in $[bmim][PF_6]$ is identical to that in water (*viz.* PYR > MePIP > MOR) and coincides with the sequence of basic strength in the amines. Fig. 2 illustrates the Brønsted plot for this reaction in $[bmim][PF_6]$, water[21] and cyclohexane.[20]

The Brønsted slope, α_{nucl}, was 0.79 ± 0.09 in water, 0.76 ± 0.01 in $[bmim][PF_6]$ and 0.69 ± 0.03 in cyclohexane. These values were independent of the reaction medium and consistent with a transition state where the nucleophilic attack occurs slightly before the N–N=O bond in the *N*-nitrososulfonamide was cleaved. Table 1 shows the bimolecular rate constants obtained in the studied ILs as well as in other molecular solvents.

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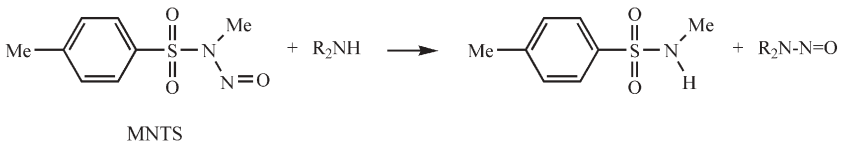

MNTS

Scheme 1

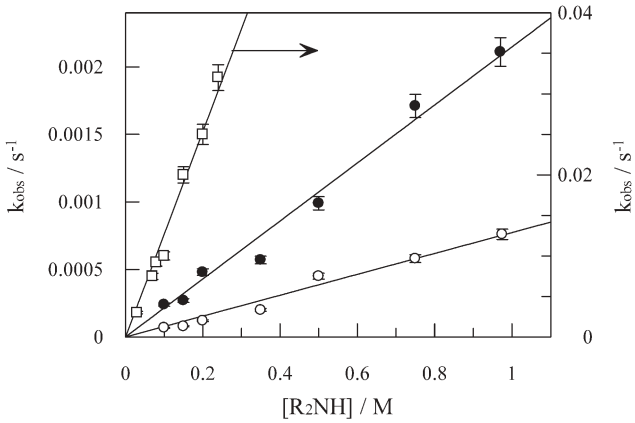

Fig. 1 Influence of the amine concentration on k_{obs} for the the nitroso group transfer from MNTS to secondary amines in [bmim][PF_6] at 25.0 °C. (○) MOR, (●) MePIP, (□) PYR.

From Table 1 it follows that the rate constant is almost independent of the ILs for those used in this study. Moreover the rate constant for nitroso group transfer in ILs is roughly one order of magnitude smaller than in water and two orders of magnitude greater than in a very low-polarity solvent such as cyclohexane. Consequently, the nucleophilicity of the amines does not increase from water to an IL. Previous studies carried out by our group[22] showed the validity of the Kamlet–Abboud–Taft equation in explaining the solvent effects on the nitroso group transfer:[23]

$$\log(k/k_0) = s\pi^* + a\alpha + b\beta \quad (1)$$

where k_0 is the rate constant in the reference solvent (cyclohexane in our case), π^* the solvent polarity/polarizability, α the hydrogen bond donating acidity of the solvent, and β its hydrogen bond accepting basicity. Fig. 3 illustrates the very good correlation between $\log(k/k_0)$ and the solvent polarity parameters for isooctane, dioxane, chloroform, methylene chloride, acetonitrile, DMSO and water (r = 0.997). It therefore seems that the effect of the solvent on this reaction is due to its dipolarity and, to a lesser extent, its ability to form hydrogen bonds *via* its own protons. The interpretation of solvent effect in terms of dipolarity and hydrogen bond acidity of the solvent can explain why the rate constant is almost independent of the IL for those used in this work.

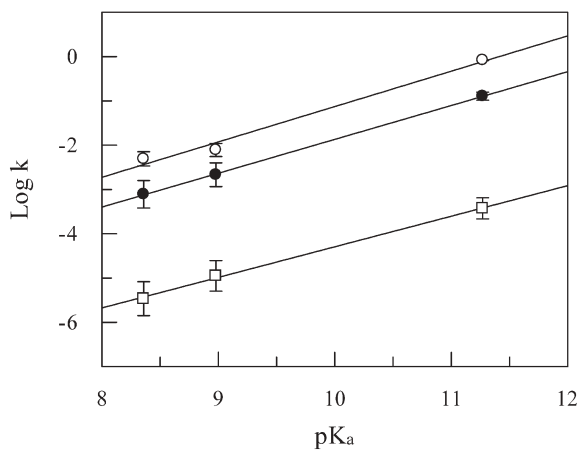

Fig. 2 Brønsted plot for the nitroso group transfer from MNTS to secondary amines in (○) water, (●) [bmim][PF_6] and (□) cyclohexane, all at 25.0 °C.

Table 1 Bimolecular rate constants for nitroso group transfer from MNTS to pyrrolidine in different solvents. Solvent polarity parameters: polarity/polarizability (π^*); hydrogen bond donating acidity (α) and hydrogen bond accepting basicity (β) are taken from ref. 15*b*

Solvent	Log k	π^*	α	β
Water	−0.081	1.09	1.17	0.47
[bmim][BF_4]	−0.903	1.047	0.627	0.376
[bmim][PF_6]	−0.896	1.032	0.634	0.207
[bmim][Tf_2N]	−0.939	0.984	0.617	0.243
[bm_2im][BF_4]	−0.889	1.083	0.402	0.363
Acetonitrile	−1.30	0.75	0.19	0.31
Cyclohexane	−3.51	0.00	0.00	0.00

Fig. 3 shows the $\log(k/k_0)$ for the different ILs in comparison with the correlation obtained for molecular solvents: $\log(k/k_0) = 2.2\pi^* + 0.9\alpha + 0.2\beta$ by using polarity parameters shown in Table 1. As can be seen the rates of nitroso group transfer in the ILs can be predicted very accurately from the reactivity in molecular solvents and the Kamlet–Abboud–Taft equation showing that no specific increase or decrease of amine nucleophilicity can be detected.

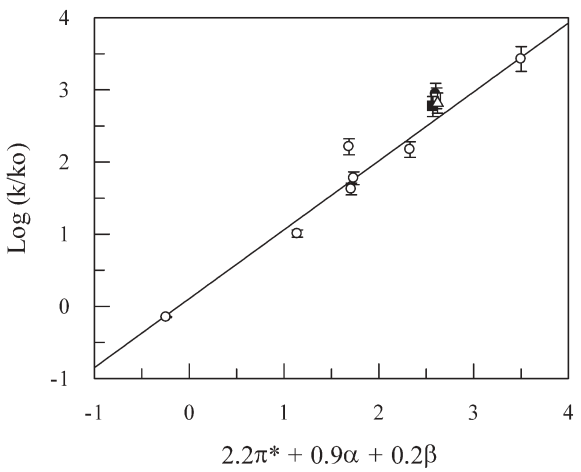

Fig. 3 Plot of $\log(k/k_0)$ against the Taft function for the nitrosation of pyrrolidine by *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in various molecular solvents. Values obtained in ILs (●) [bmim][BF_4]; (□) [bmim][PF_6]; (■) [bmim][Tf_2N] and (△) [bm_2im][BF_4] at 25.0 °C.

Previous results obtained by Welton and coworkers[17] for the aminolysis of *p*-nitrobenzenesulfonate by butylamine, dibutylamine and tributylamine in ILs: [bmpy][$N(Tf)_2$], [bmpy][OTf] and [bmim][OTf] have showed that the aminolysis rate constant is one order of magnitude faster in the ILs than in water. Moreover the aminolysis rate constant of methyl-*p*-nitrobenzenesulfonate in water was found to be roughly three times smaller than in acetonitrile. The kinetic behavior observed for the nitroso group transfer is greatly differentiated: the rate constant is 16 times greater in water than in acetonitrile. The different behavior observed for both reactions in molecular solvents should also be responsible for the different kinetic behavior observed in ILs: aminolysis of *p*-nitrobenzenesulfonate is faster in the IL than in water instead of that the nitroso group transfer is slower in the IL than in water. Therefore, available reports on reactivity in ILs must be taken reservedly and any extrapolation to other reactions requires considering the specific behaviour observed in various molecular solvents.

Acknowledgements

This work was supported by Ministerio de Ciencia y Tecnología (Project CTQ2005-04779) and Xunta de Galiza (PGIDT03-PXIC20905PN and PGIDIT04TMT209003PR). Ana Godoy thanks Xunta de Galicia for a predoctoral fellowship.

Notes and references

1 (*a*) P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley–VCH, Weinheim, 2003, pp. 174–332; (*b*) H. Olivier-Bourbigou and L. Magna, *J. Mol. Catal.*, 2002, **182–183**, 419–437.
2 (*a*) K. R. Seddon, *J. Chem. Technol. Biotechnol.*, 1997, **68**, 351–356; (*b*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071–2083; (*c*) P. Wasserscheid and W. Keim, *Angew. Chem.*, 2000, **112**, 3926; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772–3789; (*d*) *Ionic Liquids. Industrial Applications to Green Chemistry*, ACS Symp. Ser., 2002, p. 818; (*e*) S. V. Dzyuba and R. A. Bartsch, *Angew. Chem., Int. Ed.*, 2003, **42**, 148–150.
3 M. Freemantle, *Chem. Eng. News*, 1998, **76**, 32–37.
4 C. E. Song, D. Jung, S. Y. Choung, E. J. Roh and S. Lee, *Angew. Chem., Int. Ed.*, 2004, **43**, 6183–6185.
5 W. Qian, E. Jin, W. Bao and Y. Zhang, *Angew. Chem., Int. Ed.*, 2005, **44**, 952–955.
6 H. Sun, K. Harms and J. Sundermeyer, *J. Am. Chem. Soc.*, 2004, **126**, 9550–9551.
7 P. Kotrusz, S. Toma, H. G. Schmalz and A. Adler, *Eur. J. Org. Chem.*, 2004, 1577–1583.
8 D. W. Kim, C. E. Song and D. Y. Chi, *J. Am. Chem. Soc.*, 2002, **124**, 10278–10279.
9 J. K. Lee and M. J. Kim, *J. Org. Chem.*, 2002, **67**, 6845–6847.
10 J. Mo, L. Xu and J. Xiao, *J. Am. Chem. Soc.*, 2005, **127**, 751–760.
11 K. K. Laali and V. J. Gettwert, *J. Org. Chem.*, 2001, **66**, 35–40.
12 (*a*) N. L. Lancaster, T. Welton and G. B. Young, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2267–2270; (*b*) N. L. Lancaster, P. A. Salter, T. Welton and G. B. Young, *J. Org. Chem.*, 2002, **67**, 8855–8861.
13 N. L. Lancaster and T. Welton, *J. Org. Chem.*, 2004, **69**, 5986–5992.
14 (*a*) A. G. Avent, P. A. Chaloner, M. P. Day, K. R. Seddon and T. Welton, *J. Chem. Soc., Dalton Trans.*, 1994, 3405–3413; (*b*) A. K. Abdul-Sada, S. Al-Juaid, A. M. Greenway, P. B. Hitchcock, M. J. Howells, K. R. Seddon and T. Welton, *Struct. Chem.*, 1990, **1**, 391–394; (*c*) A. Elaiwi, P. B. Hitchcock, K. R. Seddon, N. Srinivasan, Y. M. Tan, T. Welton and J. A. Zora, *J. Chem. Soc., Dalton Trans.*, 1995, 3467–3472.
15 (*a*) C. P. Fredlake, M. J. Muldoon, S. N. V. K. Aki, T. Welton and J. F. Brennecke, *Phys. Chem. Chem. Phys.*, 2004, **6**, 3280–3285; (*b*) L. Crowhurst, P. R. Mawdsley, J. M. Pérez-Arlandis, P. A. Salter and T. Welton, *Phys. Chem. Chem. Phys.*, 2003, **5**, 2790–2794; (*c*) J. L. Anderson, J. Ding, T. Welton and D. W. Armstrong, *J. Am. Chem. Soc.*, 2002, **124**, 14247–14254; (*d*) A. J. Carmichael and K. R. Seddon, *J. Phys. Org. Chem.*, 2000, **13**, 591–595; (*e*) M. J. Muldoon, C. M. Gordon and I. R. Dunkin, *J. Chem. Soc., Perkin Trans. 2*, 2001, 433–435; (*f*) K. A. Fletcher, S. N. Baker, G. A. Baker and S. Pandey, *New J. Chem.*, 2003, **27**, 1706–1712; (*g*) K. A. Fletcher, I. A. Storey, A. E. Hendricks, S. Pandey and S. Pandey, *Green Chem.*, 2001, **3**, 210–215; (*h*) F. V. Bright and G. A. Baker, *J. Phys. Chem. B*, 2006, **110**, 5822–5823.
16 C. Chiappe and D. Pieraccini, *J. Org. Chem.*, 2004, **69**, 6059–6064.
17 L. Crowhurst, N. Ll. Lancaster, J. M. Pérez and T. Welton, *J. Am. Chem. Soc.*, 2004, **126**, 11549–11555.
18 L. García-Río, J. R. Leis, J. A. Moreira and F. J. Norberto, *J. Org. Chem.*, 2001, **66**, 381–390.
19 J. G. Huddleston, H. D. Willauer, R. P. Swatloski, A. E. Visser and R. D. Rogers, *Chem. Commun.*, 1998, 1765–1766.
20 L. García-Río, J. R. Leis, J. A. Moreira and D. Serantes, *Eur. J. Org. Chem.*, 2004, 614–622.
21 L. García-Río, E. Iglesias, J. R. Leis, M. E. Peña and A. Rios, *J. Chem. Soc., Perkin Trans. 2*, 1993, 29–37.
22 (*a*) L. García-Río, E. Iglesias and J. R. Leis, *J. Org. Chem.*, 1997, **62**, 4701–4712; (*b*) L. García-Río, E. Iglesias and J. R. Leis, *J. Org. Chem.*, 1997, **62**, 4712–4720.
23 (*a*) M. J. Kamlet, J. L. Abboud and R. W. Taft, *Prog. Phys. Org. Chem.*, 1981, **13**, 485–630; (*b*) M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377–383; (*c*) R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.*, 1976, **98**, 2886–2894; (*d*) M. J. Kamlet, J. L. Abboud and R. W. Taft, *J. Am. Chem. Soc.*, 1977, **99**, 6027–6038; (*e*) M. J. Kamlet, J. L. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, 1983, **48**, 2877–2887.

Brønsted acidic room temperature ionic liquids derived from *N*,*N*-dimethylformamide and similar protophilic amides†

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Received 3rd April 2006, Accepted 9th June 2006
First published as an Advance Article on the web 19th June 2006
DOI: 10.1039/b604777g

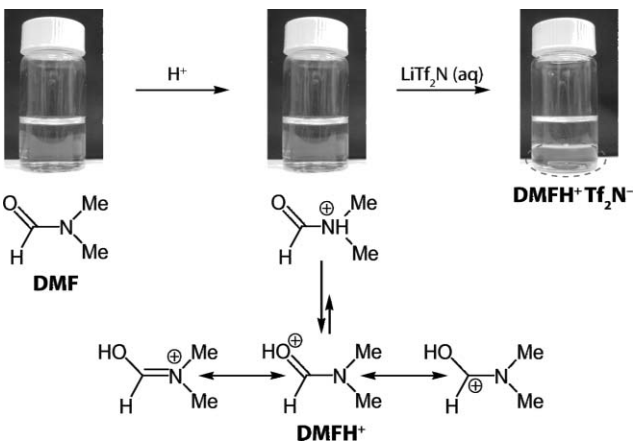
We herein describe a convenient and efficient one-pot route to a new family of cost-effective, highly proton conductive room temperature ionic liquids based on N,N-dimethylformamide and structural analogues thereof, thereby opening up potential in the fuel cell industry and other areas.

Air and water stable room temperature ionic liquids (RTILs) are rapidly gaining momentum as stable, conductive, "no vapor pressure" solvents of interest for a range of applications.[1–4] While RTILs are most commonly formed by transferring an alkyl group to a basic site on a neutral parent amine or other base through an S_N2 reaction, an important "protic" RTIL subgroup resulting from direct proton transfer between Brønsted acids and bases also exists. Ironically, in spite of the fact that the first RTIL ever reported ($EtNH_3^+$ NO_3^- by Walden in 1914)[5] was of the protic variety, aprotic ionic liquids currently dominate the open literature. This trend is likely to mend itself, however, as the potential of the application of protic RTILs in chemistry appears to be very high.[6] Indeed, their most significant contribution may well come in the form of novel electrolytes for fuel cells, batteries, double-layer capacitors, solar cells, electrochromics, and actuators.[7,8]

Polymer electrolyte membrane fuel cells (PEMFCs) are the subject of increasing interest for their role in energy renewal and clean transportation, and now appear to be the best candidates for large-scale commercialization of fuel cells.[9] To be efficient, however, PEMFCs require the use of membrane electrolytes whose properties are not totally met by the current perfluorosulfonate-based technology. For example, Nafion-type membranes require humidification for operation, limiting practical operational temperatures to under 80 °C. Thus, great interest has been focused recently on the development of alternate ionomeric proton conducting membrane systems which do not require humidification. Of key importance here is the exploration of RTILs toward "solventless" anhydrous liquid electrolyte materials.[7,8,10–12] To date, several systems showing melting points (T_m) below 100 °C and high ionic conductivities (>10^{-2} S cm^{-1} at 130 °C) have been reported for protic RTILs based on a wide variety of tertiary amine/acid pairs.[7,10,11]

Here, we describe a simple strategy to form a novel class of proton-transfer RTILs whose Brønsted bases are composed of *N*,*N*-dimethylformamide (DMF) and a series of analogs all containing an acyclic amide. Of course, DMF is a widely used conventional aprotic organic solvent with a high dielectric constant (37 at 20 °C), a low viscosity (0.8 cP at 20 °C), and a wide operational temperature range, *i.e.*, a low melting point (−61 °C) paired with a high boiling point (153 °C). We also envisaged that tautomerization of protonated DMF-like amides might lead to lower basicities and higher ionic conductivities.[13] Our strategy has yielded a new series of inexpensive RTILs that are air and water stable, hydrophobic, highly proton conductive, and are easily prepared by two steps in a single reaction vessel. Importantly, the cation precursors are all inexpensively available on an industrial scale.

As outlined in Scheme 1, the essence of our methodology is simply neutralization of a given amide base with a strong Brønsted acid followed by metathesis with an appropriate anion donor, all in aqueous media. As our choice for anion exchange, we selected the lithium salt of bis(trifluoromethylsulfonyl)imide ($LiTf_2N$) because we expected this choice to meet our requirement for low melting point, fluid RTILs. These features are attributed to the low lattice energy of Tf_2N^- salts and the negative charge of the anion being delocalized on the nitrogen and four oxygen atoms, *generally* resulting in weak coordinating strength. For example, the shape and internal flexibility of this anion seem to induce a plasticizing effect and reduce the crystallinity of linear polymers such as poly(ethylene oxide). Additionally, a feature important in designing anhydrous electrolytes is the observation that metathesis with



Scheme 1

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† Electronic supplementary information (ESI) available: Karl–Fischer coulometric moisture determinations, viscosity plot, and Walden plot. See DOI: 10.1039/b604777g

aqueous $LiTf_2N$ often affords hydrophobic RTILs which are immiscible with water and so spontaneously phase separate from the aqueous milieu. Somewhat surprisingly, this was even found to be the case for a polyamidoamine (PAMAM) dendrimer which, upon anion exchange with Tf_2N^-, formed a hydrophobic RTIL.[14]

To illustrate our basic synthetic approach, we discuss DMF as a starting material, however, all amides afforded RTILs with similar ease. The requisite protonated species, $DMFH^+\ NO_3^-$, was first obtained by neutralization of DMF in an iced 1 : 1 (v/v) mixture with water by careful titration with 2.0 M HNO_3, followed by slow dropwise addition of a further equivalent of acid. In the second step, formation of the corresponding RTIL was accomplished by a metathesis reaction of $DMFH^+\ NO_3^-$ with a molar equivalent of $LiTf_2N$ (predissolved in water). Phase separation of the hydrophobic $DMFH^+\ Tf_2N^-$ (**1**) occurred readily to form two layers on stirring. In order to drive phase separation, the two-phase system was further washed with 2.0 M HNO_3. After recovery of the lower RTIL phase, brief rotary evaporation effectively removed minor DMF and HNO_3 residues, leaving behind the desired RTIL as a nearly colorless free-flowing liquid in very high yield. Several additional RTILs were made using this method, affording the entire series of amide-based RTILs given in Scheme 2. For the RTIL syntheses reported here, the yields are essentially quantitative and are by-product free (*i.e.*, 100% atom efficiency).

The ambient temperature ionic conductivity (σ) of as-prepared **1** was found to be quite high (1.45 mS cm^{-1}), consistent with our expectations. Further treatment of **1** under vacuum at 60 °C led to a decrease in water content from 0.26(9) to 0.14(7) wt%, and a concomitant decrease in σ to 1.14 mS cm^{-1}. We note that, despite their preparation directly in water, quite remarkably, Karl–Fischer titration results reveal that RTILs **1–9** contained only 0.43(3) wt% residual water on average (see Fig. S1 in ESI†). In comparison, water levels of 4.6 to 6.0 wt% were determined for water-miscible Brønsted RTILs containing hydrophilic anions such as BF_4^- or HSO_4^-.[15] Drying of the current RTILs reduced the average water content to 0.18(6) wt%. The conductivities and additional thermophysical properties of the dried RTILs are summarized in Table 1. As can be seen, for the homologous series of formamides

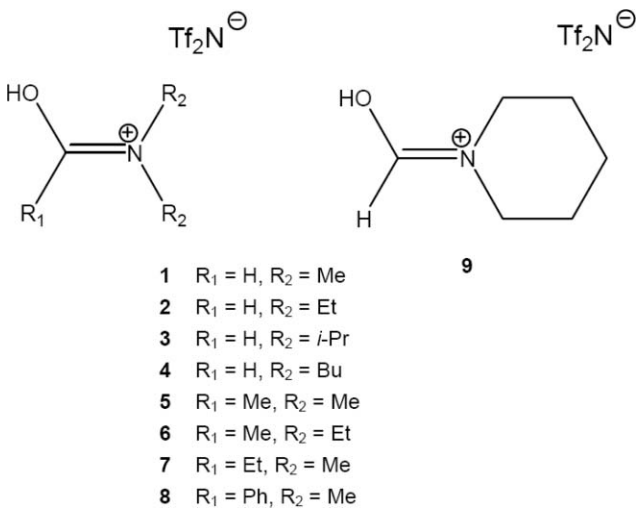
Table 1 Summary of physicochemical properties for RTILs **1–9**[a]

RTIL	density/g cm^{-3} [b]	η/cP[b]	T_d/°C[c]	σ/mS cm^{-1} [b]
1	1.553	239	189	1.14
2	1.428	130	194	1.41
3	1.334	202	189	1.09
4	1.162	101	189	0.77
5	1.507	162	232	2.81
6	1.417	138	213	1.13
7	1.468	133	236	1.94
8	1.411	599	217	0.39
9	1.496	760	216	0.28

[a] In all cases, equimolar (1 : 1) salts were prepared. [b] Determined at 23 °C. [c] Temperature of 10% overall weight loss from TGA.

1–4, the density decreases steadily from 1.553 to 1.162 as the alkyl chain (R_2) increases from one to four carbons; this general trend is expected. With the exception of **8** and **9**, these RTILs all have a relatively low viscosity (η), being in the range 100 to 200 cP at room temperature. By 100 °C, η drops below 10 cP in most cases and is only 16 cP for RTIL **9** (Fig. S2, ESI†). The detailed investigation into the dependence of the physical properties for these ILs on water and other chemical contents as well as temperature is currently underway.

The Fourier transform infrared (FTIR) spectrum of **1** was consistent with a structure composed of $DMFH^+$ and Tf_2N^- (Fig. 1). The appearance of ν_aSO_2 (1344 and 1327 cm^{-1}), ν_aCF_3 (peak at 1181 cm^{-1}, shoulder at 1230 cm^{-1}), ν_sSO_2 (1128 cm^{-1}), and ν_aSNS (1051 cm^{-1}) bands clearly indicate the presence of Tf_2N^- anions in the RTIL.[16] As suggested in Scheme 1, the reaction of neutral amides with electrophiles such as H^+ occurs on O not N because protonation at this position allows one to draw multiple resonance structures. Of course, the true structure of the cation is a weighted average of these resonance structures. As can be seen in Fig. 1, the carbonyl mode of the DMF parent molecule at 1659 cm^{-1} shifts and decreases in amplitude, while simultaneously a band at 1721 cm^{-1}, assigned to a C=N stretch, appears for $DMFH^+$.[17] This result suggests the left-most resonance structure of the bottom tautomer in Scheme 1 is the dominant one. Support for this proposal is provided in Fig. 2. The case is



Scheme 2

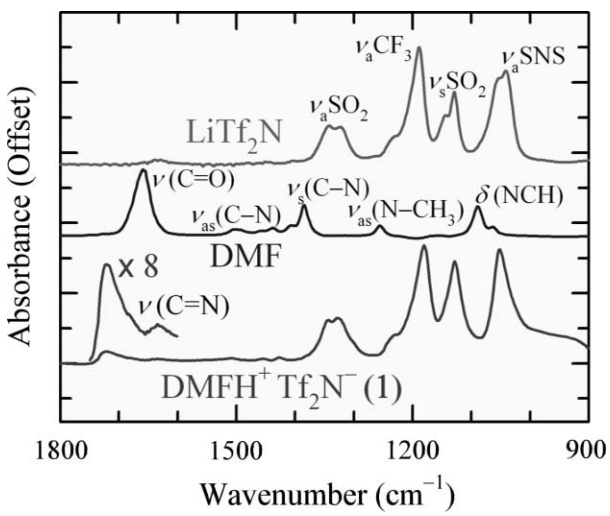


Fig. 1 FTIR spectra of the individual components of **1** and the RTIL **1**.

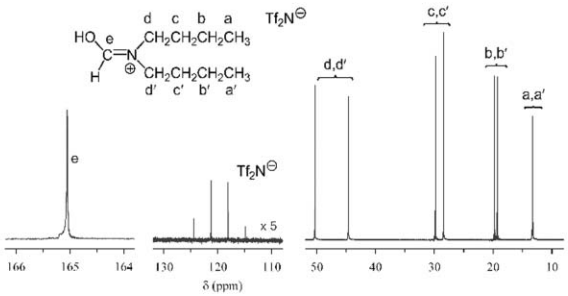


Fig. 2 Expanded regions of ^{13}C NMR (400 MHz, $CDCl_3$) spectrum of **4** revealing split resonances for the butyl chain carbons due to tautomerization.

best illustrated using RTIL **4** based on *N*,*N*-dibutylformamide (DBF). It is clearly seen that, due to the asymmetry imposed by the C=N bond, the signals assigned to the mirrored carbons of the two butyl chains do not coalesce but indeed experience greater separation with proximity to the N atom.

Thermogravimetric analysis (TGA) curves measured for all of the RTILs studied reveal a two-step weight loss process with a thermal decomposition temperature (T_d) in the ~190–235 °C range (Table 1), fully adequate for applications at or below about 150 °C. Using **4** as an example, first-derivative TGA results exhibit two well-defined minima near 220 and 375 °C (Fig. 3). Interestingly, both TGA first-derivative minima and thermal degradations depend somewhat on the choice of cation (amide) and roughly lie within a 50 °C window centered at 240 and 400 °C, respectively.

The specific conductivity of RTILs **1–9** is excellent, being in the mS cm^{-1} regime and as high as 2.81 mS cm^{-1} (for **5**) at room temperature. As shown in Fig. S3 of the ESI,† taken as a group, RTILs **1–9** generally follow the Walden rule, namely that molar conductivity is inversely proportional to the viscosity. Departure to the right of the ideal Walden line is well precedented and is indicative of ion pairing/association, presumably due to cohesive electrostatic forces but possibly some van der Waals interactions as well.[10]

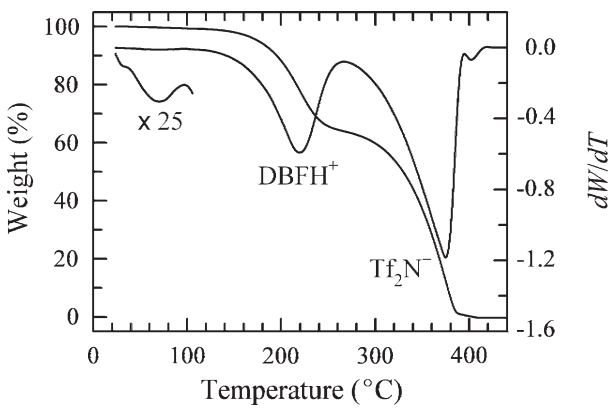


Fig. 3 TGA of **4** in N_2 performed at a scan rate of 5 °C min^{-1}. This represents the lower limit of T_d among the RTILs studied. The expanded feature in the derivative profile suggests loss of sorbed water at ~80 °C.

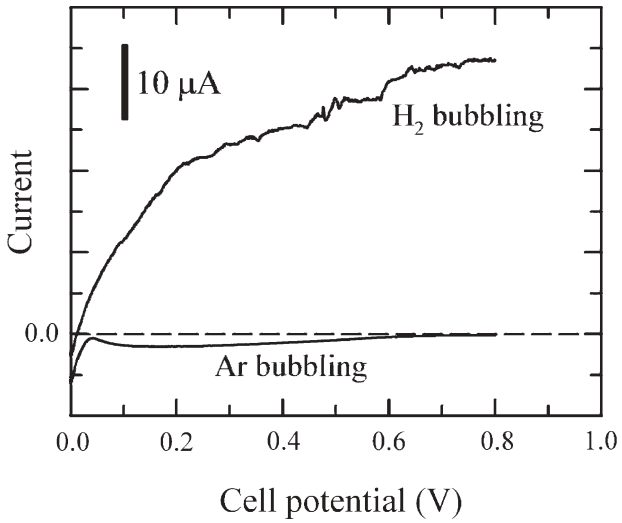


Fig. 4 Current–voltage characteristics for a proton pump cell containing **1** under H_2 or Ar sparging at 25 °C. Scan rate is 10 mV s^{-1}.

Although vehicular and Grotthus-type mechanisms of ionic conduction are both likely to be at play, direct current polarization experiments using a simple proton pump cell confirmed the fact that protonic conduction indeed takes place within RTILs **1–9**.‡ The cell design came from previously reported work.[11] Typical results of such a proton pump experiment using RTIL **1** as a representative case are shown in Fig. 4. As can be seen, the current detected under anodic argon bubbling remained quite low. Conversely, a significant current enhancement was observed upon switching to a hydrogen atmosphere. Furthermore, the evolution of H_2 gas bubbles at the cathode was visually confirmed in accordance with the cathodic reaction $DMFH^+ + e^- \rightarrow DMF + \frac{1}{2}H_2(g)$. In a control experiment, no enhancement of polarization current nor cathodic H_2 generation was observed in the conventional RTIL 1-ethyl-3-methylimidazolium Tf_2N under anode exposure to an H_2 atmosphere. The high conductivity and the enhancement of polarization current under H_2 thus support proton conduction in **1**. Similar results were observed for the other RTILs as well. Taken together, our results suggest a high practical value for these new RTILs in devising protic amphoteric conductors under non-humidifying conditions, with possible application in other areas (*e.g.*, sensory elements, thermal fluids) as well.

Acknowledgements

This work was conducted at the Oak Ridge National Laboratory and supported by Basic Energy Sciences and EMSP, U.S. Department of Energy, under contract No. DE-AC05-00OR22725. JFH acknowledges ORISE for a postdoctoral fellowship. GAB acknowledges generous support from a Wigner Fellowship.

Notes and references

‡ Direct current polarization was performed with a CH Instruments Model 604 B electrochemical analyzer. Experiments were conducted in a Faraday cage and used a U-shaped glass tube cell composed of two 0.5 mm Pt wire electrodes. The introduction of the desired gas in the vicinity of the anode

was achieved using PTFE tubing. The electrodes were pretreated by repetitive cathodic and anodic polarization in 2.0 M H_2SO_4.

1 *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2003.
2 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **29**, 3772; G. A. Baker, S. N. Baker, S. Pandey and F. V. Bright, *Analyst*, 2005, **130**, 800; J. H. Davis, *Chem. Lett.*, 2004, **33**, 1072.
3 J. S. Wilkes, J. A. Levisky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263; J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965.
4 P. Bonhôte, A.-P. Dias, N. Papageorgiou, K. Kalyanasundaram and M. Grätzel, *Inorg. Chem.*, 1996, **35**, 1168.
5 P. Walden, *Bull. Acad. Imper. Sci. (St. Petersbourg)*, 1914, 1800.
6 A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 5962; Z. Du, Z. Li, S. Guo, J. Zhang, L. Zhu and Y. Deng, *J. Phys. Chem. B*, 2005, **109**, 19542.
7 *Electrochemical Aspects of Ionic Liquids*, ed. H. Ohno, John Wiley & Sons, Hoboken, New Jersey, 2005.
8 R. Hagiwara, T. Nohira, K. Matsumoto and Y. Tamba, *Electrochem. Solid-State Lett.*, 2005, **8**, A231; M. A. Navarra, S. Panero and B. Scrosati, *Electrochem. Solid-State Lett.*, 2005, **8**, A324; P.-Y. Chen and C. L. Hussey, *Electrochim. Acta*, 2004, **49**, 5125; R. F. de Souza, J. C. Padilha, R. S. Gonçalves and J. Dupont, *Electrochem. Commun.*, 2003, **5**, 728; D. R. MacFarlane, P. Meakin, J. Sun, N. Amini and M. Forsyth, *J. Phys. Chem. B*, 1999, **103**, 4146; R. E. Del Sesto, G. A. Baker, S. N. Baker, B. L. Scott, T. S. Keizer, A. K. Burrell and T. M. McCleskey, *Chem. Commun.*, 2006, 272.
9 J. Larminie and A. Dicks, *Fuel Cell Systems Explained*, 2nd edn, John Wiley & Sons, Chichester, 2003.
10 M. Yoshizawa, W. Xu and C. A. Angell, *J. Am. Chem. Soc.*, 2003, **125**, 15411; W. Xu and C. A. Angell, *Science*, 2003, **302**, 422.
11 A. Noda, M. A. B. H. Susan, K. Kudo, S. Mitsushima, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2003, **107**, 4024; M. A. B. H. Susan, A. Noda, S. Mitsushima and M. Watanabe, *Chem. Commun.*, 2003, 938.
12 M. Yoshizawa and H. Ohno, *Chem. Commun.*, 2004, 1828; M. Hirao, H. Sugimoto and H. Ohno, *J. Electrochem. Soc.*, 2000, **147**, 4168.
13 G. Alberti, M. Casciola, E. D'Alessandro and M. Pica, *J. Mater. Chem.*, 2004, **14**, 1910; K. R. Jeffrey, G. Z. Zukowska and J. R. Stevens, *J. Chem. Phys.*, 2003, **119**, 2422; A. M. Grillone, S. Panero, B. A. Retamal and B. Scrosati, *J. Electrochem. Soc.*, 1999, **146**, 27.
14 J.-F. Huang, H. Luo, C. Liang, I.-W. Sun, G. A. Baker and S. Dai, *J. Am. Chem. Soc.*, 2005, **127**, 12784; J. -F. Huang, H. M. Luo and S. Dai, *J. Electrochem. Soc.*, 2006, **153**, J9.
15 H. Xing, T. Wang, Z. Zhou and Y. Dai, *Ind. Eng. Chem. Res.*, 2005, **44**, 4147.
16 I. Rey, P. Johansson, J. Lindgren, J. C. Lassègues, J. Grondin and L. Servant, *J. Phys. Chem. A*, 1998, **102**, 3249.
17 Y. A. Fadeeva, L. I. Demina, Y. G. Gorbunova, L. E. Shmukler, L. P. Safonova and A. Y. Tsivadze, *Russ. J. Coord. Chem.*, 2003, **29**, 551.

Preparation of simple ammonium ionic liquids and their application in the cracking of dialkoxypropanes

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Received 3rd January 2006, Accepted 9th May 2006
First published as an Advance Article on the web 25th May 2006
DOI: 10.1039/b600041j

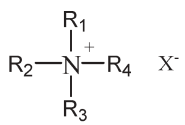
Owing to the unique advantages of ionic liquids, the preparation and industrial application of ionic liquids have attracted considerable interest. Herein, we report that a series of simple ammonium ionic liquids has been synthesized and characterised. These ionic liquids are air and water stable, easy to prepare from amine and acid, and relatively cheap. They have been used as catalysts and environmentally benign solvents for the cracking reactions of dialkoxypropanes, eliminating the need for volatile organic solvents and additional catalysts. The results clearly demonstrate that these ionic liquids can be easily separated and reused without losing their activity and quality. Furthermore, the conversion and selectivity obtained with this method are significantly increased in comparison with those reported in traditional organic solvents to date. These ionic liquids provide a good alternative way for the synthesis of alkoxypropenes.

Introduction

Ionic liquids have attracted considerable interest as environmentally friendly or "green" alternatives to conventional molecular organic solvents because they have very low vapor pressure and are non-explosive and thermally stable in a wide temperature range.[1,2] Furthermore, they are often immiscible with organic solvents because of their polar nature and may therefore be used in biphasic systems. Now ionic liquids have been used as environmentally benign solvents or catalysts for a number of chemical processes,[3] such as separations,[4] reactions,[5] homogeneous two-phase catalysis,[6] and polymerizations.[7] The current emphasis on alternative reaction media is motivated by the need for efficient methods for replacing toxic or hazardous solvents and catalysts. The use of ionic liquids as alternative reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem.[8]

Notwithstanding the unique advantages of ionic liquids as reaction media and catalysts, currently they have not been widely applied in industry. The reason for this is probably related to the high cost of ionic liquids, the difficulty in separation or recycling, the paucity of data with regard to their toxicity and biodegradability, and so on. Recently, some new ionic liquids have been prepared *via* a simple and atom-economic acid–base neutralization reaction. For example, Noda *et al.*[9] reported the preparation and application of the Brønsted acid–base ionic liquids from imidazole and bis(trifluoromethanesulfonyl) amide. Han *et al.*[10] prepared new ionic liquids by neutralization of 1,1,3,3- tetramethylguanidine with different acids. However, the preparation of simple ammonium ionic liquid *via* acid–base neutralization from cheap amine and acid is absence in the literature. After the announcement of the first industrial process involving ionic liquids by BASF (BASIL[11] process) in 2003 the potential of ionic liquids for new chemical processes and technologies is beginning to be recognized. Recently, Weyershausen and co-workers[12] reported the industrial application of ionic liquids as performance additives and process aids. Furthermore, we[13] have succeeded in the industrial synthesis of cinnamic acid using sulfate ionic liquids as solvents and catalysts, which are applied by the Juhua Group Corporation Lanxi Agricultural Chemistry Factory. Continuing our investigations in this area, herein we reported the preparation and application of some simple ammonium ionic liquids in the synthesis of alkoxypropenes, Scheme 1.

Alkoxypropenes are a highly valuable class of fine chemicals with applications in polymer formulations, surfactants and drug delivery systems as well as general organic syntheses.[14,15] They are important intermediates in the synthesis of clarithromycin, β-ionone, vitamin A, vitamin E, and so on.[16] Several methods have been reported to prepare alkoxypropenes: for example, the reaction of alkynes or allenes with alcohols,[17] pyrolysis or catalytic cracking reaction of dialkoxypropanes.[18] However, the application of these methods is limited because the reaction must be carried out under severe conditions at elevated temperature and high pressure,[19] or calls for the use of volatile organic solvents and toxic catalysts.[20] Recently, we[21] reported the cracking reaction of dialkoxypropanes in chloride—aluminium chloride ionic liquids eliminate the need for volatile organic solvents and additional catalysts. However, the cost of imidazolium ionic liquids is high, and these chloroaluminate ionic liquids are extremely sensitive to water and are corrosive to many



$R_{1,2,3}$=H,Me,Et,Pr,Bu; X=H_2PO_4,HSO_4,BF_4

Scheme 1 The structures of simple ammonium ionic liquids.

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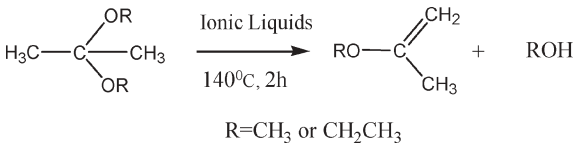
materials because of the presence of aluminium chloride. Despite numerous attempts to overcome these drawbacks, no benign methods have appeared for the synthesis of alkoxypropenes so far.

We describe here the cracking reaction of dialkoxypropanes to synthesize alkoxypropenes in simple ammonium ionic liquids, Scheme 2. These ionic liquids are air and water stable, and easy to prepare from cheap amines. In addition, they are relatively cheap compared with the imidazolium ionic liquids. Hence these ionic liquids are used as solvents and catalysts for the cracking reaction of dialkoxypropanes, eliminating the need for a volatile organic solvent and additional catalyst. The conversion and yield obtained with this method are significantly increased in comparison with those reported in traditional organic solvents to date. In particular, these ionic liquids are very easy to be separated and reused.



Scheme 2 The cracking reaction of dialkoxypropanes in the ionic liquids.

Experimental

Materials

Dimethoxypropane (99%) and diethoxypropane (99%) were provided by Zhejiang Jubang Hi-Tech Corporation. Acetic acid, sulfuric acid, phosphoric acid, tetraflouroboric acid, nitric acid, trimethylamine, diethylamine, triethylamine, n-tripropylamine, iso-propylamine, n-tributylamine, n-butylamine, n-butyl bromide, imidazole and 1-methylimidazole were all used as received unless otherwise stated.

Instruments

The NMR spectra of the ionic liquids and alkoxypropenes were recorded with a 500 MHz Bruker spectrometer in DMSO, $CDCl_3$ and calibrated with tetramethylsilane (TMS) as the internal reference. The purity of raw materials and alkoxypropenes was analysized using a Shang Feng GC112A gas chromagraphy fitted with a SE-30 column (30 m, 025 μm diameter) and a flame ionisation detector. The structure and the purtiy of the products were further identified using a HP6890 GC/MS spectrometer by comparing retention times and fragmentation patterns with authentic samples. Infrared spectra measurements were performed on a Nicolet 470 FT-IR spectrometer using KBr optics. Differential scanning calorimetry was carried out on a Netzsch STA 409 PG/PC.

Synthesis of ionic liquids

The simple ammonium ionic liquids of general type [amine][H_2PO_4] were synthesized in the following way.

Triethylammonium dihydrogen phosphate [Et_3NH][H_2PO_4]. The synthesis of ionic liquid was carried out in a 500 ml round-bottomed flask, which was immersed in a recirculating heated water-bath and fitted with a reflux condenser. In a typical reaction, phosphoric acid (98 g, 1.0 mol) 85% solution was dropped into the triethylamine (101 g, 1.0 mol) at 60 °C in 1 hour. After the addition, the reaction mixture was stirred for an addition period of 2 hours at 70 °C to ensure the reaction had proceeded to completion. Water was removed by heating the residue at 80 °C in high vacuum (5 mm Hg) until the weight of the residue remained constant. The yield of [Et_3NH][H_2PO_4] was 99% (198 g). ^{1}H NMR (DMSO-d_6): δ (ppm) 1.18 (t, 9H), 3.10 (m, 6H), 8.89 (s, 1H). Melting point: 93 °C.

The following dihydrogen phosphates were synthesized as [Et_3NH][H_2PO_4].

Trimethylammonium dihydrogen phosphate [Me_3NH][H_2PO_4]. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.55 (s, 9H), 2.76 (s, 1H). Melting point: 116 °C.

Diethylammonium dihydrogen phosphate [Et_2NH_2][H_2PO_4]. ^{1}H NMR (DMSO-d_6): δ (ppm) 1.16 (t, 6H), 2.92 (m,3H), 8.18 (s, 2H). Melting point: 148 °C.

The ammonium ionic liquids of general type [amine] [HSO_4] were synthesized in the following way.

Triethylammonium sulfate [Et_3NH][HSO_4]. The synthesis of ionic liquid was carried out in a 500 ml round-bottomed flask, which was immersed in a recirculating heated water-bath and fitted with a reflux condenser. Sulfuric acid (98 g, 1.0 mol) 98% solution in water was dropped into the triethylamine (101 g, 1.0 mol) at 60 °C in 1 hour. After the addition, the reaction mixture was stirred for an addition period of 1 hour at 70 °C to ensure the reaction had proceeded to completion. Then the traces of water was removed by heating the residue at 80 °C in high vacuum (5 mm Hg) until the weight of the residue remained constant. The yield of [Et_3NH][HSO_4] was 99% (198 g). ^{1}H NMR (DMSO-d_6): δ (ppm) 1.18 (t, 3H), 3.10 (m, 2H), 8.89 (s, 1H). Melting point: 91 °C.

The following sulfates were synthesized as [Et_3NH][HSO_4].

Trimethylammonium sulfate [Me_3NH][HSO_4]. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.55 (s, 9H), 2.76 (s, 1H). Melting point: 129 °C.

Diethylammonium sulfate [Et_2NH_2][HSO_4]. ^{1}H NMR (DMSO-d_6): δ (ppm) 1.16 (t, 6H), 2.92 (m,3H), 8.18 (s, 2H). Melting point: 82 °C.

n-Tripropylammonium sulfate [Pr_3NH][HSO_4]. ^{1}H NMR (DMSO-d_6): δ (ppm) 0.90 (t, 9H), 1.63 (m, 6H), 2.99 (m, 6H), 9.15 (s, 1H). Melting point: 92 °C.

n-Tributylammonium sulfate [Bu_3NH][HSO_4]. ^{1}H NMR (DMSO-d_6): δ (ppm) 0.91 (t, 9H), 1.31 (m, 6H), 1.58 (m, 6H), 3.00 (m, 6H), 8.32 (s, 1H). Melting point: 80 °C.

The other ammonium ionic liquids were synthesized in the following way.

Triethylammonium tetrafluoroborate [Et_3NH][BF_4]. The synthesis of ionic liquid was carried out in a 250 ml

round-bottomed flask, which was immersed in a recirculating heated water-bath and fitted with a reflux condenser. Tetrafluoroboric acid (43.5 g, 0.5 mol) 40% solution in water was dropped into the triethylamine (50.5 g, 0.5 mol) at 60 °C for 2 hours. After the addition, the reaction mixture was stirred for 2 hours at 80 °C to ensure the reaction had proceeded to completion. Then water was removed by heating the residue at 80 °C in high vacuum (5 mm Hg) until the weight of the residue remained constant. The yield of $[Et_3NH][BF_4]$ was 99% (93 g). δ_H (DMSO) 1.18 (t, 9H), 3.10 (m, 6H), 8.89 (s, 1H). Melting point: 98 °C.

Triethylammonium Acetate $[Et_3NH][CH_3COO]$. The synthesis of ionic liquid was carried out in a 250 ml round-bottomed flask, which was immersed in a recirculating heated water-bath and fitted with a reflux condenser. Acetic acid (30.0 g, 0.5 mol) was dropped into the triethylamine (50.5 g, 0.5 mol) at 60 °C in 2 hours. After the addition, the reaction mixture was stirred for 2 hours at 80 °C to ensure the reaction had proceeded to completion. The reaction mixture was dried at 80 °C in high vacuum (5 mm Hg) until the weight of the residue remained constant. The yield of liquid [Et3NH][CH3COO] was 98% (79 g). ^{1}H NMR (DMSO-d_6): δ (ppm) 1.18 (t, 9H), 2.10 (s, 3H), 3.10 (m, 6H), 8.89 (s, 1H).

Other ionic liquids used in this paper were synthesized according to standard literature methods.[22]

Cracking reaction of dialkoxypropanes in ionic liquids

The cracking reactions of dialkoxypropanes were investigated in several different ionic liquids. These reactions were carried out in a 250 ml volumetric flask set in a recirculating heated oil-bath and stirred with a magnetic stir bar. In a typical reaction, 2,2-dimethoxypropane (66 g, 0.5 mol) was added slowly to triethylammonium dihydrogen phosphate ionic liquid (99 g, 0.5 mol) at 140 °C under stirring for several hours. During the reaction, 2-methoxypropene and methanol were evolved from the surface of the reaction mixture, collected in a cold trap and analysed by gas chromatograph (typical data are listed in Table 1). It should be noted that the addition of the dialkoxypropane shoud be slow, letting the reaction take place on the surface of the ionic liquid, then most of the alkoxypropene and alcohol could be evaporated from the surface immediately.

Results and discussion

In this work, we prepared a series of simple ammonium ionic liquids from cheap amine and acid. Then these ionic liquids were used as catalysts and environmentally benign solvents for the cracking reactions of dialkoxypropanes.

Preparation of simple ammonium ionic liquids

A great deal of attention has been given to imidazolium ionic liquids in the past several years.[23] However, the industrial application of these ionic liquids is limiting because of the high price of imidazolium ionic liquids.[12] Therefore, some non-imidazolium ionic liquids have drawn much attention, such as phosphonium and ammonium ionic liquids. In this article, we would like to draw attention to ammonium ionic liquids. Here we synthesized a series of simple ammonium ionic liquids from cheap amine and acid.

Table 2 lists the results of preparation of these simple ammonium ionic liquids. It was seen that the preparation of simple ammonium ionic liquids was direct and simple, and the yield was all higher than 98%. In the preparation of ammonium ionic liquids, no solvent is needed, eiminating the need of volatile organic solvents such as dichloromethane and acetonitrile used in some reported ionic liquids.[24] The melting points of these ionic liquids were investigated by differential scanning calorimetry. The results show the melting point was strongly affected by the anion of the ionic liquid. Among these ionic liquids, triethylammonium acetate is liquid at room temperature. Furthermore, all of the ionic liquids reported are at least partially soluble in water as well as alcohols, and are immiscible with non-polar solvents such as cyclohexane and petroleum ether. The cost of these ionic liquids is relatively cheap in comparison with ionic liquids reported to date. Considering the lower cost and the solventless syhthesis of these ionic liquids, we conclude that the simple ammonium ionic liquids are one of the most attractive ionic liquids from an industrial point of view.

Cracking reaction of dialkoxypropanes in ionic liquids

The cracking reaction appeared to be dependent on ionic liquids used for a given temperature and time. The correlative data are listed in Table 1. It was clear that the catalytic activity was strongly affected by the anion of the ionic liquids. The

Table 1 The cracking reaction of 2,2-dimethoxypropane in ionic liquids

Entry	Solvents	T/°C	Conversion[a] (%)	Selectivity (%)
1	$[Et_3NH][H_2PO_4]$	140	46	95
2	$[Me_3NH][H_2PO_4]$	140	51	93
3	$[Me_3NH][HSO_4]$	140	81	93
4	$[Et_3NH][BF_4]$	140	15	81
5	$[Et_3NH][CH_3COO]$	140	24	85
6	[Hmim][HSO_4]	140	75	89
7	[Bmim][HSO_4]	140	81	90
8	Trichlorobenzene + *p*-toluenesulfonic acid	200	43	79

[a] Conversion after 2 hours.

Table 2 The results of preparation of simple ammonium ionic liquids[a]

Entry	ionic liquids	T^a/°C	Time/h	Yield (%)
1	$[Et_3NH][H_2PO_4]$	60–70	3	99
2	$[Me_3NH][H_2PO_4]$	50–70	3	98
3	$[Et_2NH_2][H_2PO_4]$	50–70	3	99
4	$[Et_3NH][HSO_4]$	60–70	2	99
5	$[Me_3NH][HSO_4]$	50–70	2	99
6	$[Et_2NH_2][HSO_4]$	50–70	2	99
7	$[Pr_3NH][HSO_4]$	70–80	2	99
8	$[Bu_3NH][HSO_4]$	70–80	2	99
9	$[Et_3NH][BF_4]$	60–80	4	99
10	$[Et_3NH][CH_3COO]$	60–80	4	98

[a] Reaction temperature.

good conversion and yield were obtained with the $[HSO_4]$ anion. However, when a salt with a tetrafluoroborate anion such as $[Et_3NH][BF_4]$ was used, the reaction was much slower and therefore the conversion of product was significantly lower than those obtained with $[HSO_4]$ anion. While dihydrogen phosphate anion was used, although the selectivity of the reaction was much higher, the conversion of dimethoxypropane was lower than those obtain with $[Me_3NH][HSO_4]$ because of the weaker acidity of the phosphate ionic liquid. The results show the cracking reactions of the dialkoxypropane are affected by the acidity of ionic liquids. The better yields could be obtained when the strongly acidic ionic liquids are used. Above all, the yield of alkoxypropene was obtained better results in sulfate ionic liquids, which are significantly increased in comparison with those in halohydrocarbon as solvent and p-toluenesulfonic acid as catalyst.

An important feature of these reactions in the sulfate ionic liquids is that there is no evidence for significant formation of side reaction. However, when the liquid cracking reaction was carried out in the presence of p-toluenesulfonic acid, the side products such as p-toluenesulfonic acid methyl ester, acetone and methyl ether would be formed.

In order to obtain higher yield, five kinds of sulfate ionic liquids were used in the cracking reaction. Table 3 shows the effect of the cation of ionic liquid on the conversion and the selectivity of the cracking reaction. We could find that $[Et_3NH][HSO_4]$ might be the best for the cracking reaction of alkoxypropane in all the ammonium ionic liquids. The reason maybe related to the acid property of the ammonium ionic liquids. The acid property of the ammonium ionic liquid would decrease when the number of the carbon of the ionic liquids increases.

It should be noted that the influence of the quantity and the temperature on the reaction was great. Firstly, we investigated the influence of quantity of $[Et_3NH][HSO_4]$, which was recorded from 0.15 mol to 1.00 mol. As can be seen in Table 4, the more $[Et_3NH][HSO_4]$ was used, the higher was the conversion of alkoxypropenes. However, the result did not continue improving when the quantity was 0.50 mol or greater. Secondly, the temperature appeared to affect the reaction greatly. Low temperature (120 °C) led to poor conversion levels. When the temperature of the cracking reaction was higher than 160 °C, the selectivity would decrease largely, because of the formation of methyl ether and acetone. In contrast, the desired alkoxypropenes were obtained with good results at 140 °C.

The raw materials and products of the reaction are all volatile compounds, so the separation of products and ionic liquids is very easy. Once the reaction is completed, heating is sufficient to remove products from the ionic liquids. The ionic liquids could be recycled after the products were distilled off. It had been used for ten times for the cracking reaction of dimethoxypropane to produce methoxypropene. Table 5 shows that the conversion and the selectivity did not reduce after it was reused ten times. It seemed that $[Et_3NH][HSO_4]$ could have the potential to be used more than ten times.

Table 3 The cracking reaction of 2,2-dimethoxypropane in sulfate ionic liquids

Entry	Solvent	T/°C	Conversion[a] (%)	Selectivity (%)
1	$[Me_3NH][HSO_4]$	140	81	93
2	$[Et_3NH][HSO_4]$	140	82	95
3	$[Et_2NH_2][HSO_4]$	140	84	90
4	$[Pr_3NH][HSO_4]$	140	76	92
5	$[Bu_3NH][HSO_4]$	140	71	89

[a] Conversions after 2 hours.

Table 4 Effect of the temperature and the quantity of $[Et_3NH][HSO_4]$ ionic liquid to the cracking reaction[a]

Entry	Quantity/mol	T/°C	Conversion[b] (%)	Selectivity (%)
1	0.15	140	75	89
2	0.25	140	80	92
3	0.50	140	82	95
4	0.75	140	82	94
5	1.00	140	83	95
6	0.50	160	85	87
7	0.50	180	89	71
8	0.50	120	72	94
9	0.50	100	27	90
10[c]	0.50	140	85	93

[a] The quantity of 2,2-dimethoxypropane was 0.5 mol. [b] Conversions after 2 hours. [c] 2,2-Diethoxypropane was used.

Table 5 Effect of reused $[Et_3NH][HSO_4]$ ionic liquid for the cracking reaction of dimethoxypropane

Entry	Recycling	T/°C	Conversion[a] (%)	Selectivity (%)
1	0	140	82	95
2	1	140	84	92
3	2	140	82	94
4	3	140	81	95
5	4	140	83	93
6	5	140	82	95
7	6	140	80	96
8	7	140	82	95
9	8	140	83	95
10	9	140	81	94

[a] Conversion after 2 hours.

Conclusion

For the industrial application, ionic liquids are usually expensive compared to the traditional organic solvents. In this paper, a series of simple ammonium ionic liquids were synthesized and characterised, which are water insensitive, relatively cheap and easy to prepare. Considering the lower cost and the solventless synthesis of these ionic liquids, we could conclude that the simple ammonium ionic liquids are very attractive in industry. These ionic liquids are used in the cracking reaction of dialkoxypropanes to alkoxypropenes without the use of traditional volatile organic compounds and additional catalysts. The reactions process well in sulfate ionic liquids and alkoxypropenes are obtained with high conversion and selectivity, especially in the $[Et_3NH][HSO_4]$ ionic liquids. The effect of the ionic liquids, temperature, quantity and recycling on the conversion and selectivity is discussed. Good conversion and high yield of alkoxypropenes could be obtained with a 1 : 1 mole ratio under 140 °C for 2 hours in the $[Et_3NH][HSO_4]$ ionic liquid. These ionic liquids provide a good alternative way for the industry synthesis of alkoxypropenes.

Acknowledgements

This work was supported by Natural Science Foundation of China (NO.20434020 and NO. 20573093).

References

1 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792; R. Sheldon, *Green Chem.*, 2005, **7**, 267; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3773.
2 J. S. Wilkes, J. A. Levisky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263; J. S. Wilkes and M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.*, 1992, 965.
3 T. Welton, *Chem. Rev.*, 1999, **99**, 2071; J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667.
4 J. G. Huddleston, H. D. Willauer, R. P. Swatloski, A. E. Visser and R. D. Rogers, *Chem. Commun.*, 1998, 1765; J. Esser, P. Wasserscheid and A. Jess, *Green Chem.*, 2004, **6**, 316.
5 R. Sheldon, *Chem. Commun.*, 2001, 2399; C. J. Adams, M. J. Earle, G. Roberts and K. R. Seddon, *Chem. Commun.*, 1998, 2097.
6 A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac and K. R. Seddon, *Org. Lett.*, 1999, **1**, 997.
7 R. T. Carlin and J. S. Wilkes, *J. Mol. Catal. A: Chem.*, 1990, **63**, 125.
8 F. C. Liu, M. B. Abrams, R. T. Baker and W. Tumas, *Chem. Commun.*, 2001, 433; E. D. Bates, R. D. Mayton, I. Ntai and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 926; M. J. Earle, P. B. McCormac and K. R. Seddon, *Green Chem.*, 2000, **2**, 261; G. A. Olah, T. Mathew, A. Goeppert, B. Torok, I. Bucsi, X. Y. Li, Q. Wang, E. R. Marinez, P. Batamack, R. Aniszfeld and G. K. S. Prakash, *J. Am. Chem. Soc.*, 2005, **127**, 5964.
9 A. Noda, M. Susan, K. Kudo, S. Mitsushima, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2003, **107**, 4024.
10 H. Gao, B. Han, J. Li, T. Jiang, Z. Liu, W. Wu, Y. Chang and J. Zhang, *Synth. Commun.*, 2004, **34**, 3083.
11 M. Maase, K. Massonne, K. Halbritter, R. Noe, M. Bartsch, W. Siegel, V. Stegmann, M. Flores, O. Huttenloch and M. Becher, *EP Pat.*, EP 1 472 201, 2004.
12 B. Weyershausen and K. Lehmann, *Green Chem.*, 2005, **7**, 15; B. Weyershausen, K. Hell and U. Hesse, *Green Chem.*, 2005, **7**, 283.
13 J. Weng, C. Wang, H. Li and Y. Wang, *Green Chem.*, 2006, **8**, 96.
14 V. R. Choudhary, V. H. Rane and A. M. Rajput, *Ind. Eng. Chem. Res.*, 2000, **39**, 904.
15 W. G. S. Reyntjens and E. Goethals, *Polym. Adv. Technol.*, 2001, **12**, 107; E. M. Carreira, W. Lee and R. A. Singer, *J. Am. Chem. Soc.*, 1995, **117**, 3649.
16 S. Frauchiger and A. Baiker, *Appl. Catal., A*, 2003, **253**, 33; J. R. Behling, P. Farid, I. Khanna, J. R. Medich, M. Prunier, M. G. Scaros and R. M. Weier, *US Pat.*, US 5 151 519, 1999.
17 M. Bosch and M. Schlaf, *J. Org. Chem.*, 2003, **68**, 6225; J. H. Teles, N. Rieber, K. Breuer, D. Demuth, H. Hibst, H. Etarodt and U. Rheude, *US Pat.*, US 6 221 416, 2001.
18 N. B. Lorette, W. L. Howard and J. H. Brown, *J. Org. Chem.*, 1959, **24**, 1731; W. Juergen, L. Peter and S. Helmut, *EP Pat.*, EP 0 490 221, 1992.
19 S. Krill, S. Kretz, V. Hafner and G. Markowz, *US Pat.*, US 6 566 559, 2001; J. H. Teles, N. Rieber, K. Breuer, D. Demuth, H. Hibst and A. Hagemeyer, *US Pat.*, US 6 060 035, 1998.
20 Y. Okimotom, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2002, **124**, 1590; D. Toni, H. Eckhard and K. Herbert, *EP Pat.*, EP 0 197 283, 1986.
21 Y. Wang, H. Li, C. Wang and H. Jiang, *Chem. Commun.*, 2004, 1938.
22 G. Y. Zhao, T. Jiang, H. X. Gao, B. X. Han, J. Huang and D. H. Sun, *Green Chem.*, 2004, **6**, 75; Lauric Ropel, S. B. Lionel, N. V. K. A. Sudhir, A. S. Mark and J. F. Brennecke, *Green Chem.*, 2005, **7**, 83.
23 C. J. Bradaric, A. Downard, C. Kennedy, A. J. Robertson and Y. Zhou, *Green Chem.*, 2003, **5**, 143.
24 W. Wu, W. Li, B. Han, Z. Zhang, T. Jiang and Z. Liu, *Green Chem.*, 2005, **7**, 701; J. D. Hobrey, W. M. Reichert, R. P. Swatloski, G. A. Broker, W. R. Pitner, K. R. Seddon and R. D. Rogers, *Green Chem.*, 2002, **4**, 407.

Mannich-type reactions in water using anionic water-soluble calixarenes as recoverable and reusable catalysts

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Received 17th March 2006, Accepted 22nd May 2006
First published as an Advance Article on the web 12th June 2006
DOI: 10.1039/b603962f

Mannich-type reactions in water can be carried out without the need for any added surfactants and organic solvents. The water-soluble calix[4]resorcinarene sulfonic acid, 2,8,14,20-tetramethyl-5,11,17,23-tetrakis(sulfomethyl)calix[4]resorcinarene, which functions as an efficient inverse phase-transfer catalyst, can be recovered as an aqueous solution and recycled after the simple extraction of the water-insoluble products.

Introduction

The 'greening' of global chemical processes has became a major issue in the chemical industry.[1] Organic reactions in water without using harmful organic solvents have attracted a great deal of interest in both academic and industrial research because, in addition to environmental concerns, there are beneficial effects of aqueous solvents on rates and selectivities of important organic transformations.[2] Among such reaction systems, aqueous biphasic reaction systems using water-soluble catalysts have the practical advantage that the catalysts can be reused after simple decantation or extraction of the water-insoluble products, provided that the catalysts show high catalytic activity in water.

We recently developed a new reaction system,[3] which is based on the inverse phase-transfer catalysis[4,5] of water-soluble calix[*n*]arenes. For example, alkylation reactions of active methylene compounds, alcohols and phenols with alkyl halides proceed smoothly in aqueous NaOH solution without the need for any added organic solvent, using water-soluble calix[*n*]arenes, *p*-(trimethylammoniomethyl)calix[*n*]arene methyl ethers (*n* = 4, 6 and 8), as catalysts,[3b,d] as do the aldol-type condensation and Michael addition reactions of activated methyl and methylene compounds.[3c]

Two research groups[6,7] have recently reported on Mannich-type reactions in water with either polar water-miscible organic solvents (co-solvents)[6a,d] or surfactants[6b–e,7] using Brønsted acid catalysis to produce β-amino carbonyl compounds.[8,9] The efficiency of Brønsted acid catalysis prompted us to explore a new catalytic system for Mannich-type reactions in water without the need for any added co-solvents or surfactants.[10] Our working hypothesis was that water-soluble calixarene sulfonic acids[11,12] could be used as inverse phase-transfer catalysts[4,5] to facilitate the reactions through the formation of a host–guest complex, with a nucleophile component in the organic–aqueous interfacial layer or the bulk aqueous phase. Herein, we disclose the practical examples of carbon–carbon bond formation by Mannich-type reactions in water that utilize anionic water-soluble calixarenes as the inverse phase-transfer catalysts. The latter can easily be prepared in only two steps, followed by an ion exchange reaction. Furthermore, this reaction system offers an environmental advantage in that no waste water contaminated with organic solvents is produced, because the aqueous catalyst solution can be recovered and recycled after the simple extraction of the water-insoluble products.

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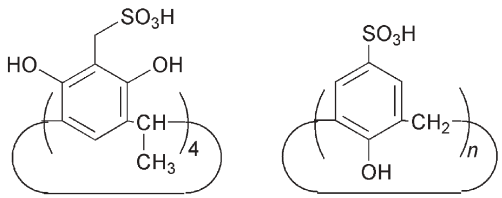
Results and discussion

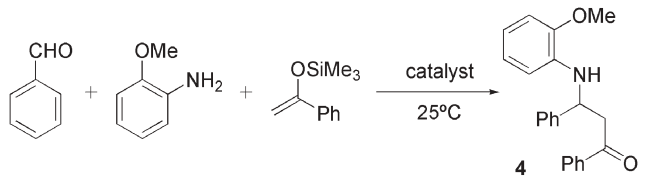
The catalytic activity of water-soluble calixarene sulfonic acids (Fig. 1), 2,8,14,20-tetramethyl-5,11,17,23-tetrakis(sulfomethyl)-calix[4]resorcinarene, **1**, and *p*-sulfocalix[*n*]arenes, **2** (*n* = 4)[13] and **3** (*n* = 6),[13] was first tested in model three-component Mannich-type reactions in water, and the results are summarized in Table 1. Treatment of benzaldehyde with *o*-anisidine and 1-phenyl-1-(trimethylsiloxy)ethene in water for 8 h at 25 °C afforded only a very small amount of the desired product, 3-(2-methoxyphenyl)amino-1,3-diphenyl-1-propanone (5%, Entry 1). The addition of *p*-toluenesulfonic acid (*p*-TsOH) to the reaction mixture resulted in a slight increase (4%) in the yield (9%, Entry 6). Interestingly, in the presence of calixarene sulfonic acids **2** and **3**, the yield of the product increased to 48% (Entry 7) and 44% (Entry 8), respectively. If one molecule of calix[4]arene sulfonic acid **2** is considered to correspond to four molecules of *p*-TsOH, the yield of **4** can be calculated as 21% for **2**. This difference in the yield might have resulted from high "local" proton concentration around the molecule of **2** and/or its ability to form a host–guest complex. Moreover, when the same reaction was carried out in the



1 **2** (*n* = 4) **3** (*n* = 6)

Fig. 1 Water-soluble calixarene sulfonic acids **1**, **2** and **3**.

Table 1 Mannich-type reactions in the presence of various catalysts in water[a]



Entry	Catalyst (mol%)	Time/h	Yield (%)[b]
1	none	8	5
2	**1** (10)	8	81
3[c]	**1** (10)	3	89
4[d]	**1** (5)	8	65
5	**1** (1)	8	33
6	*p*-TsOH (10)	8	9
7	**2** (10)	8	48
8	**3** (10)	8	44
9	DBSA (10)	2	88
10	HBF_4 (10) + SDS (10)	2	87

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), silyl enolate (1.5 mmol), catalyst (0.10 mmol in the case of 10 mol%), H_2O (2 mL), 800 rpm. [b] Isolated yield. [c] Ultrasonic irradiation. [d] H_2O (1 mL).

presence of the calix[4]resorcinarene sulfonic acid **1**, the yield increased to 81% (Entry 2). The increase in the yield to such an extent is attributable to hydroxyl groups on the resorcinol rings and/or methylene groups between the rings and sulfo groups in the catalyst **1**. The methylene groups make the cavity deeper and render the wide-rim more hydrophobic. For purposes of comparison, typical micellar catalysts such as *p*-dodecylbenzenesulfonic acid (DBSA) and a combination of HBF_4 and sodium dodecyl sulfate (SDS) were also examined under the same conditions, except for the reaction time, giving the desired product in good yields, as has already been reported (Entries 9, 10).[6,7] Although a prolonged reaction time was required in the case of catalyst **1** compared to DBSA and HBF_4 plus SDS, the selectivity was comparable. The use of ultrasonic irradiation led to a considerable reduction in reaction time (Entry 3).

We next examined the possibility of recovering and reusing the calix[4]resorcinarene sulfonic acid **1** in water. These results are summarized in Table 2. After extraction of the products with ethyl acetate, the aqueous catalyst solution was recovered, and could be reused directly in the next cycle. It is indeed remarkable that the activity of the catalyst **1** was retained after being consecutively recycled, even in the fifth run, and that the yields are practically identical to that observed when fresh catalyst is used (Entries 1–5).[14] On the other hand, when DBSA and HBF_4 plus SDS were used as catalysts, a significant decrease in yields with consecutive catalytic cycles was observed, which can be attributed to the difficulty associated with product separation and catalyst recovery due to emulsion formation (Entries 6–11).[15] Although all of the three catalytic systems constitute a white turbid reaction mixtures, in the case of **1** the reaction mixture immediately forms two immiscible layers upon treatment with ethyl acetate. Thus, additional procedures such as centrifugation[9f] are unnecessary to recover and reuse this type of catalyst from the reaction mixture. In comparison, in a Mannich-type reaction system using indium

Table 2 Recovery and reuse of various catalysts in Mannich-type reaction in water[a]

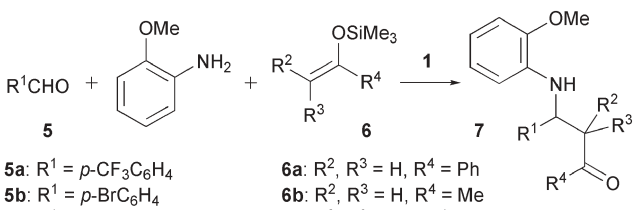
Entry	Catalyst	Time/h	Yield (%)[b,c]
1	**1** (1st use)	8	81
2	**1** (2nd use)	8	83
3	**1** (3rd use)	8	82
4	**1** (4th use)	8	83
5	**1** (5th use)	8	81
6	DBSA (1st use)	2	78
7	DBSA (2nd use)	2	27
8	DBSA (3rd use)	2	5
9	HBF_4 + SDS[d] (1st use)	2	73
10	HBF_4 + SDS[d] (2nd use)	2	70
11	HBF_4 + SDS[d] (3rd use)	2	35

[a] Reaction conditions: benzaldehyde (1.0 mmol), *o*-anisidine (1.0 mmol), 1-phenyl-1-(trimethylsiloxy)ethene (1.5 mmol), catalyst (0.10 mmol), water (2 mL), 25 °C, 800 rpm. [b] Isolated yield. [c] For extraction procedure (EtOAc 10 mL × 2), see the Experimental section. [d] 0.10 mol.

trichloride as a Lewis acid catalyst and water as a solvent, the catalyst can be recycled only when the reaction is complete.[9b,e]

This new catalytic system, using calix[4]resorcinarene sulfonic acid **1** was found to be applicable to the reaction of several substrates using silyl enolates as nucleophilic components. The results are summarized in Table 3. In all cases the desired products were obtained in good yields. Unlike DBSA which failed to yield the products,[7c] cyclohexanecarbaldehyde also functioned quite well as a substrate, affording the desired products with **1** (Entry 4). When a water-sensitive substrate such as ketene silyl acetal **6c** was used, a lower temperature and excess amount of the silyl enolate (3.0 equiv.) were required to produce a good yield of the desired adduct (Entry 8).[6a,b,d,7a,c]

Table 3 Mannich-type reactions catalyzed by **1** in water using silyl enolates as nucleophiles[a]



5 6 7

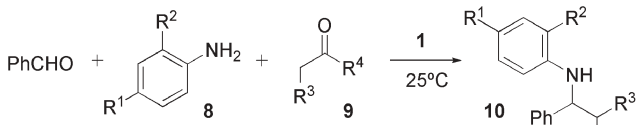
5a: R^1 = *p*-$CF_3C_6H_4$
5b: R^1 = *p*-BrC_6H_4
5c: R^1 = *o*-$MeOC_6H_4$
5d: R^1 = *c*-Hexyl
5e: R^1 = Me_2CHCH_2
5f: R^1 = PhCO
5g: R^1 = Ph

6a: R^2, R^3 = H, R^4 = Ph
6b: R^2, R^3 = H, R^4 = Me
6c: R^2, R^3 = Me, R^4 = OMe

Entry	Aldehyde	Enolate	Temp./°C	Product	Yield (%)[b]
1	**5a**	**6a**	25	**7a**	73
2	**5b**	**6a**	25	**7b**	72
3	**5c**	**6a**	25	**7c**	72
4	**5d**	**6a**	25	**7d**	82
5[c]	**5e**	**6a**	0	**7e**	64
6	**5f**	**6a**	0	**7f**	80
7[d]	**5g**	**6b**	0	**7g**	77
8[d]	**5g**	**6c**	0	**7h**	80

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), silyl enolate (1.5 mmol), catalyst **1** (0.10 mol), H_2O (2 mL), 8 h, 800 rpm. [b] Isolated yield. [c] The aldehyde was slowly added to the reaction mixture during 6 h, and then the whole was stirred for 2h. [d] Silyl enolate (3.0 mmol).

Table 4 Mannich-type reactions catalyzed by **1** in water using ketones as nucleophilic substrates[a]



8a: R^1, R^2 = H
8b: R^1 = OMe, R^2 = H
8c: R^1 = H, R^2 = OMe
8d: R^1 = Cl, R^2 = H

9a: R^3, R^4 = $-(CH_2)_4-$
9b: R^3, R^4 = $-(CH_2)_3-$
9c: R^3, R^4 = $-CH_2O(CH_2)_2-$
9d: R^3 = H, R^4 = Et

Entry	Amine	Ketone	Product	Yield (%)[b]	*syn:anti*[c]
1[d]	**8a**	**9a**	**10a**	95	25 : 75
2	**8b**	**9a**	**10b**	92	22 : 78
3	**8c**	**9a**	**10c**	92	40 : 60
4	**8d**	**9a**	**10d**	96	32 : 68
5	**8a**	**9b**	**10e**	48	25 : 75
6	**8a**	**9c**	**10f**	85	29 : 71
7[e]	**8a**	**9d**	**10g** + **10h**	76[f]	39 : 61[g]

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), ketone (5.0 mmol), catalyst **1** (0.10 mmol), H_2O (2 mL), 8 h, 800 rpm. [b] Isolated yield as a mixture of diastereomers. [c] The diastereomeric ratio was determined by ^{1}H NMR analysis at 400 MHz. [d] Catalyst **1** (0.01 mmol). [e] 50 °C, 16 h. [f] Regioisomeric ratio; major (**10g**):minor (**10h**) = 53 : 47. [g] Diastereomeric ratio of minor product (**10h**).

We then pursued the direct use of ketones instead of silyl enolates,[7b,c] and found that these are also suitable for use. The results are shown in Table 4. Three-component Mannich-type reactions in water using cyclohexanone as a nucleophilic component afforded the Mannich bases in high yields (Entries 1–4). For the reaction of benzaldehyde with aniline and cyclohexanone, only 1 mol% of the catalyst **1** was required (Entry 1). The reaction of 2-butanone also gave the desired adduct in good yield, although a longer reaction time and higher temperature were required for completion (Entry 7).

Taking into account the size and/or shape of the protonated imine and nucleophile molecules, the nucleophiles are more suitable than the protonated imines as guests for inclusion in the cavity of **1**. Thus, it is most likely that the water-soluble calix[4]resorcinarene sulfonic acid **1** would be expected to form host–guest complexes with nucleophile molecules in the organic–aqueous interfacial layer, and the attack of the nucleophile (silyl enolate or enol form of the ketone) on the protonated imine would take place in the interfacial layer (Fig. 2). This is somewhat different from the Makosza interfacial mechanism of normal phase-transfer catalysis, which involves a C–C bond-forming reaction within the bulk organic phase as a final step.[16] The interfacial mechanism of inverse phase-transfer catalysis has been elucidated in our previous papers.[3c,d] For instance, in *o*-alkylations of alcohols with alkyl halides in aqueous NaOH solution, the water-soluble calix[*n*]arenes, *p*-(trimethylammoniomethyl)calix-[*n*]arene methyl ethers (*n* = 4, 6 and 8), form host–guest complexes with alkoxide anions in the bulk aqueous phase or the organic–aqueous interfacial layer, and nucleophilic attack by the anion on an alkyl halide takes place in the interfacial layer.

On the other hand, it is difficult to rule out the following possibility. The water-soluble calix[4]resorcinarene sulfonic acid **1** could transport both the imine and nucleophile molecules into the aqueous phase through the formation of iminium ion pair complex and inclusion complex, respectively, and the reaction of the nucleophile component with the protonated imine could take place in the organic–aqueous interfacial layer. If the effect of cavity size of calix[*n*]resorcinarene sulfonic acids on the catalytic efficiency could have been investigated in the reactions of various substrates, a more clear understanding of the mechanism of the reaction would be conceivable. To the best of our knowledge, no method exists for selective synthesis of calix[*n*]resorcinarenes with $n \geqslant 5$, despite continuing efforts to realize it.[17] In either event, this calix[4]resorcinarene sulfonic acid **1** functions not only as an Brønsted acid catalyst but also an inverse phase-transfer catalyst. That is to say, the catalyst **1** performs dual functional catalysis.[18]

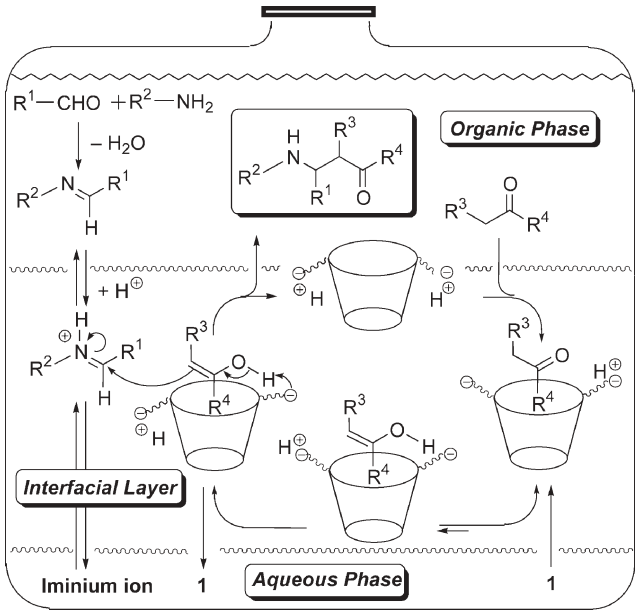


Fig. 2 Possible mechanism of a Mannich-type reaction, catalyzed by water-soluble calixarene sulfonic acid **1**.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400s spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ with tetramethylsilane as an internal standard, and *J* values are given in Hz. The MS spectra were measured on a JEOL JMS-600 mass spectrometer (EI, 70 eV). IR spectra were recorded on a Bio-Rad FTS-60A spectrometer. Preparative gel-permeation chromatography (GPC) was done with a JAI model 908 liquid chromatograph with a couple of JAIGEL-1H and 2H columns.

Materials

The calix[4]resorcinarene sulfonic acid **1** was obtained by passing an aqueous solution of the sodium salt of **1**, prepared according to the literature methods,[19] through an

ion-exchange column of Amberlyst 15 in the hydrogen form, and was identified by IR and NMR spectroscopy. *p*-Sulfocalix[*n*]arenes **2** (n = 4) and **3** (n = 6) were prepared following literature methods.[13] Sodium dodecyl sulfate (SDS) and *p*-dodecylbenzenesulfonic acid (DBSA) were purchased from E. Merck and Kanto Chemicals, respectively, and used without further purification. Unless otherwise noted, starting materials, substrates and catalysts were commercially available materials and were used without further purification.

Procedure for Mannich-type reactions

Aldehyde (1.0 mmol), amine (1.0 mmol), silyl enolate or ketone (1.5 mmol) were successively added to a solution of calix[4]resorcinarene sulfonic acid **1**·6H_2O (0.10 mmol in the case of 10 mol%) in water (3 mL). The mixture was stirred at 25 °C for 2–8 h with a magnetic stirring bar (ϕ 4 × 10 mm) at 800 rpm. After the addition of saturated aqueous $NaHCO_3$ (10 mL), the resulting mixture was extracted with ethyl acetate (10 mL × 4). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The products were purified by preparative GPC.

In a recycling experiment, after a reaction time of 2–8 h for each cycle, ethyl acetate (3 mL) was added to the reaction mixture, and the solution was stirred for 5 min with a magnetic stirring bar. The resulting mixture was then allowed to stand for 15 min, and the organic phase was then transferred *via* a syringe. This extraction procedure was repeated twice. The remaining aqueous catalyst solution was reused directly in the next cycle.

3-(*N*-2-Methoxyphenylamino)-1,3-diphenyl-1-propanone (4)[9f]

Colorless prismatic crystals, mp 113–114 °C (from ethanol); ν_{max} (KBr)/cm^{-1} 3414, 3060, 2946, 2867, 1674, 1272, 1233, 1026 and 737; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.51 (2 H, d, *J* 6.5), 3.84 (3 H, s), 4.97 (1 H, br s), 5.05 (1 H, t, *J* 6.5), 6.45 (1 H, dd, *J* 7.8 and 1.5), 6.62 (1 H, ddd, *J* 7.7, 7.7 and 1.5), 6.70 (1 H, ddd, *J* 7.7, 7.7 and 1.4), 6.75 (1 H, dd, *J* 7.8 and 1.4), 7.22 (1 H, dddd, *J* 7.3, 7.3, 1.8 and 1.8), 7.31 (2 H, ddd, *J* 7.8, 7.3 and 1.8), 7.42–7.45 (4 H, m), 7.55 (1 H, dddd, *J* 7.4, 7.4, 1.4 and 1.4) and 7.90–7.92 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 46.70, 54.34, 55.50, 109.43, 111.29, 116.86, 121.10, 126.42, 127.27, 128.19, 128.63, 128.75, 133.27, 136.82, 143.14, 146.98 and 197.90; *m*/*z* (EI) 331 (M^+, 86%), 212 (100), 105 (83) and 77 (63).

3-(*N*-2-Methoxyphenylamino)-1-phenyl-3-(4-trifluoromethylphenyl)-1-propanone (7a)

Colorless plate crystals, mp 149–150 °C (from methanol); ν_{max} (KBr)/cm^{-1} 3418, 3064, 3009, 2938, 2837, 1688, 1326, 1226, 1123, 1066 and 732; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.48 (1 H, dd, *J* 16.6 and 5.7), 3.55 (1 H, dd, *J* 16.6 and 7.0), 3.85 (3 H, s), 5.03 (1 H, br s), 5.11 (1 H, dd, *J* 7.0 and 5.7), 6.37 (1 H, dd, *J* 7.7 and 1.6), 6.64 (1 H, ddd, *J* 7.6, 7.6 and 1.6), 6.70 (1 H, ddd, *J* 7.6, 7.6 and 1.5), 6.76 (1 H, dd, *J* 7.7 and 1.5), 7.44 (2 H, dd, *J* 7.7 and 7.7), 7.54–7.58 (5 H, m) and 7.89–7.92 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 46.42, 53.91, 55.49, 109.54, 111.25, 117.34, 121.09, 125.70, 125.71, 125.75, 126.90, 128.15, 128.72, 133.51, 136.40, 136.58, 147.02, 147.40 and 197.25; *m*/*z* (EI) 399.1455 (M^+, $C_{23}H_{20}F_3NO_2$ requires 399.1446), 399 (87%), 280 (100), 120 (28), 105 (54) and 77 (34).

3-(4-Bromophenyl)-3-(*N*-2-methoxyphenylamino)-1-phenyl-1-propanone (7b)

Colorless crystals, 171–172 °C (from THF-hexane); ν_{max} (KBr)/cm^{-1} 3418, 3064, 2997, 2938, 2833, 1685, 1519, 1306, 1222, 1021, 735 and 688; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.45 (1 H, dd, *J* 16.5 and 5.9), 3.51 (1 H, dd, *J* 16.5 and 6.9), 3.84 (3 H, s), 4.96 (1 H, br s), 5.01 (1 H, dd, *J* 6.9 and 5.9), 6.39 (1 H, dd, *J* 7.7 and 1.5), 6.64 (1 H, ddd, *J* 7.7, 7.7 and 1.5), 6.71 (1 H, ddd, *J* 7.8, 7.8 and 1.4), 6.75 (1 H, dd, *J* 7.8 and 1.4), 7.32 (2 H, d, *J* 8.5), 7.41–7.46 (4 H, m), 7.56 (1 H, dddd, *J* 7.4, 7.4, 1.1 and 1.1) and 7.89–7.91 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 46.49, 53.78, 55.49, 109.47, 111.31, 117.19, 120.97, 121.07, 128.16, 128.27, 128.70, 131.83, 133.43, 136.48, 136.66, 142.25, 146.98 and 197.47; *m*/*z* (EI) 409.0652 (M^+, $C_{22}H_{20}BrNO_2$ requires 409.0677), 411 (28%), 409 (M^+, 26), 292 (82), 290 (100), 120 (19), 105 (54) and 77 (28).

3-(2-Methoxyphenyl)-3-(*N*-2-methoxyphenylamino)-1-phenyl-1-propanone (7c)

Dark brown oil; ν_{max} (neat)/cm^{-1} 3422, 3068, 3007, 2942, 2839, 1691, 1244, 1028 and 736; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.28 (1 H, dd, *J* 15.3 and 8.4), 3.64 (1 H, dd, *J* 15.3 and 4.4), 3.84 (3 H, s), 3.92 (3 H, s), 5.21 (1 H, br s), 5.31 (1 H, dd, *J* 8.4 and 4.4), 6.36 (1 H, dd, *J* 7.8 and 1.4), 6.57 (1 H, ddd, *J* 7.7, 7.7 and 1.4), 6.67 (1 H, ddd, *J* 7.7, 7.7 and 1.3), 6.72 (1 H, dd, *J* 7.8 and 1.3), 6.84–6.89 (2 H, m), 7.19 (1 H, ddd, *J* 7.5, 7.5 and 1.6), 7.37 (1 H, dd, *J* 7.5 and 1.6), 7.42 (2 H, dd, *J* 7.3 and 7.3), 7.52 (1 H, dddd, *J* 7.3, 7.3, 1.4 and 1.4) and 7.98–8.01 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 44.80, 49.92, 55.29, 55.52, 109.40, 110.38, 111.12, 116.48, 120.90, 121.05, 127.41, 128.11, 128.35, 128.50, 130.16, 133.08, 136.76, 136.86, 147.02, 156.55 and 198.63; *m*/*z* (EI) 361.1661 (M^+, $C_{23}H_{23}NO_3$ requires 361.1678), 361 (M^+, 15%), 242 (88), 207 (100), 105 (49) and 77 (38).

3-Cyclohexyl-3-(*N*-2-methoxyphenylamino)-1-phenyl-1-propanone (7d)

Colorless needles, mp 98–99 °C (from ethanol); ν_{max} (KBr)/cm^{-1} 3435, 3056, 2925, 2854, 1676, 1601, 1514, 1446, 1223, 1027 and 742; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.06–1.27 (5 H, m), 1.64–1.78 (5 H, m), 1.91–1.94 (1 H, m), 3.10 (1 H, dd, *J* 16.6 and 5.4), 3.23 (1 H, dd, *J* 16.6 and 6.1), 3.81 (3 H, s), 3.97–4.01 (1 H, m), 4.36 (1 H, br s), 6.59 (1 H, dd, *J* 7.6 and 7.6), 6.65 (1 H, d, *J* 7.8), 6.73 (1 H, d, *J* 7.8), 6.81 (1 H, dd, *J* 7.6 and 7.6), 7.43 (2 H, dd, *J* 7.5 and 7.5), 7.53 (1 H, dd, *J* 7.2 and 7.2) and 7.91 (2 H, d, *J* 7.7); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.34, 26.37, 26.49, 29.10, 29.82, 40.90, 42.19, 54.01, 55.46, 109.58, 110.15, 115.90, 121.35, 128.07, 128.54, 132.97, 137.22, 137.50, 146.76 and 199.40; *m*/*z* (EI) 337.2056 (M^+, $C_{22}H_{27}NO_2$ requires 337.2042), 337 (M^+, 30%), 254 (100), 218 (22), 149 (14), 105 (96) and 77 (23).

3-(*N*-2-Methoxyphenylamino)-5-methyl-1-phenyl-1-hexanone (7e)

Colorless needles, 83–84 °C (from methanol); ν_{max} (KBr)/cm^{-1} 3430, 3064, 2961, 1676, 1516, 1222, 1029 and 739; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.93 (6 H, dd, *J* 6.6 and 6.6), 1.44–1.57 (2 H, m), 1.77–1.88 (1 H, m), 3.08 (1 H, dd, *J* 16.6 and 7.7), 3.24 (1 H, dd, *J* 16.6 and 3.9), 3.82 (3 H, s), 4.12–4.19 (1 H, m), 4.22 (1 H, br s), 6.63 (1 H, ddd, *J* 7.7, 7.7 and 1.4), 6.67 (1 H, dd, *J* 7.9 and 1.4), 6.75 (1 H, dd, *J* 7.9 and 1.3), 6.84 (1 H, ddd, *J* 7.7, 7.7 and 1.3), 7.42 (2 H, dd, *J* 7.4 and 7.4), 7.53 (1 H, dddd, *J* 7.4, 7.4, 1.4 and 1.4) and 7.89–7.92 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 22.00, 23.34, 25.01, 43.65, 45.08, 47.41, 55.39, 109.61, 109.98, 116.16, 121.40, 128.02, 128.54, 133.03, 137.03, 137.31, 146.87 and 199.51; *m*/*z* (EI) 311.1891 (M^+, $C_{20}H_{25}NO_2$ requires 311.1885), 311 (M^+, 70%), 254 (54), 192 (100), 105 (57) and 77 (18).

2-(*N*-2-Methoxyphenylamino)-1,4-diphenyl-1,4-pentanedione (7f)

Light yellow cubes, mp 106–107 °C (from methanol); ν_{max} (KBr)/cm^{-1} 3355, 3043, 2930, 2829, 1682, 1514, 1222, 1030 and 742; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.45 (1 H, dd, *J* 17.5 and 4.8), 3.68 (1 H, dd, *J* 17.5 and 7.2), 3.80 (3 H, s), 4.92 (1 H, d, *J* 7.6), 5.74–5.79 (1 H, m), 6.70–6.78 (2 H, m), 6.86–6.90 (2 H, m), 7.41–7.47 (4 H, m), 7.52–7.58 (2 H, m), 7.91–7.94 (2 H, m) and 8.06–8.08 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 40.78, 53.39, 55.48, 110.00, 110.55, 117.85, 121.31, 128.19, 128.59, 128.72, 128.83, 133.40, 133.49, 135.24, 135.93, 136.49, 147.50, 198.07 and 198.73; *m*/*z* (EI) 359.1520 (M^+, $C_{23}H_{21}NO_3$ requires 359.1521), 359 (M^+, 6%), 254 (86), 236 (27), 108 (24), 105 (100) and 77 (47).

4-(*N*-2-Methoxyphenylamino)-4-phenyl-2-butanone (7g)

Colorless needles, mp 60–62 °C (from diethyl ether-hexane); Found: C, 75.65; H, 7.09. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; ν_{max} (KBr)/cm^{-1} 3418, 3066, 2940, 2836, 1718, 1702, 1514, 1232, 1027 and 739; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.09 (3 H, s), 2.90 (1 H, dd, *J* 15.9 and 5.8), 2.96 (1 H, dd, *J* 15.9 and 7.3), 3.84 (3 H, s), 4.85–4.88 (2 H, m), 6.42 (1 H, dd, *J* 7.7 and 1.4), 6.62 (1 H, ddd, *J* 7.7, 7.7 and 1.4), 6.70 (1 H, ddd, *J* 7.7, 7.7 and 1.3), 6.74 (1 H, dd, *J* 7.8 and 1.3), 7.19–7.22 (1 H, m), 7.29 (2 H, dd, *J* 7.5 and 7.5) and 7.34–7.36 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 30.61, 51.68, 54.01, 55.46, 109.41, 111.22, 116.93, 121.08, 126.26, 127.27, 128.73, 136.60, 142.71, 146.92 and 206.73; *m*/*z* (EI) 269 (M^+, 79%), 213 (41), 212 (100), 196 (21), 131 (27), 123 (31), 120 (29), 108 (38), 103 (30) and 77 (25).

Methyl 3-(*N*-2-methoxyphenylamino)-2,2-dimethyl-3-phenyl-propanoate (7h)[9f]

Colorless needles, mp 124–125 °C (from methanol); ν_{max} (KBr)/cm^{-1} 3425, 3064, 2988, 2951, 1730, 1512, 1341, 1253, 1026 and 743; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.20 (3 H, s), 1.25 (3 H, s), 3.66 (3 H, s), 3.88 (3 H, s), 4.56 (1 H, d, *J* 7.5), 5.32 (1 H, d, *J* 7.4), 6.32 (1 H, dd, *J* 7.8 and 1.5), 6.55 (1 H, ddd, *J* 7.7, 7.7 and 1.5), 6.64 (1 H, ddd, *J* 7.7, 7.7 and 1.3), 6.72 (1 H, dd, *J* 7.8 and 1.3) and 7.18–7.29 (5 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 20.62, 24.14, 47.19, 52.02, 55.62, 64.01, 109.37, 110.86, 116.28, 121.05, 127.35, 127.92, 128.28, 136.94, 139.36, 146.88 and 176.94; *m*/*z* (EI) 313.1681 (M^+, $C_{19}H_{23}NO_3$ requires 313.1678), 313 (M^+, 23%), 213 (51), 212 (100), 196 (22), 120 (12) and 91 (12).

2-[Phenyl(*N*-phenylamino)methyl]cyclohexanone (10a)[6d,9g]

Light brown solid; ν_{max} (KBr)/cm^{-1} 3385, 3027, 2946, 1696, 1604, 1513, 1496, 1453, 1290 and 754; δ_H (400 MHz; $CDCl_3$; Me_4Si; **A** (*syn*)/**B** (*anti*) = 25/75) 1.54–2.01 (6 H, m), 2.25–2.32 (1 H, m), 2.37–2.43 (1 H, m), 2.70–2.78 (1 H, m), 4.61 (0.75 H, d, *J* 7.1, for **B**), 4.68 (1 H, br s), 4.79 (0.25 H, d, *J* 4.4, for **A**), 6.51–6.55 (2 H, m), 6.58–6.64 (1 H, m), 7.02–7.07 (2 H, m), 7.16–7.20 (1 H, m), 7.25–7.29 (2 H, m) and 7.32–7.36 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si; **A**/**B** = 25/75) (for **A**) 24.78, 26.96, 28.58, 42.35, 56.56, 57.14, 114.00, 117.59, 126.94, 127.46, 128.32, 128.96, 141.53, 147.46 and 211.28; (for **B**) 23.58, 27.85, 31.24, 41.71, 57.42, 57.87, 113.54, 117.42, 127.11, 127.21, 128.42, 129.01, 141.67, 147.20 and 212.81; *m*/*z* (EI) 279.1616 (M^+, $C_{19}H_{21}NO$ requires 279.1623), 279 (M^+, 82%), 212 (48), 183 (98), 182 (100), 180 (53), 104 (48) and 77 (59).

2-[*N*-4-Methoxyphenylamino(phenyl)methyl]-cyclohexanone (10b)[7b]

Dark brown solid; ν_{max} (KBr)/cm^{-1} 3368, 3029, 2939, 2865, 1708, 1513, 1241, 1036, 823 and 701; δ_H (400 MHz; $CDCl_3$; Me_4Si; **A** (*syn*)/**B** (*anti*) = 22/78) 1.51–2.04 (6 H, m), 2.26–2.36 (1 H, m), 2.40–2.48 (m, 1H), 2.68–2.79 (m, 1H), 3.66 (2.34 H, s, for **B**), 3.67 (0.66 H, s, for **A**), 4.38 (1 H, br s), 4.54 (0.78 H, d, *J* 7.4, for **B**), 4.73 (0.22 H, d, *J* 4.1, for **A**), 6.47–6.52 (2 H, m), 6.63–6.68 (2 H, m) and 7.18–7.36 (5 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si; **A**/**B** = 22/78) (for **A**) 24.90, 27.09, 28.41, 42.43, 55.64, 56.75, 58.10, 114.56, 115.55, 126.92, 127.50, 128.33, 141.65, 141.71, 152.21 and 211.55; (for **B**) 23.64, 27.91, 31.21, 41.74, 55.64, 57.53, 58.93, 114.62, 115.12, 127.14, 127.35, 128.45, 141.37, 141.84, 152.09 and 213.01; *m*/*z* (EI) 309.1733 (M^+, $C_{20}H_{23}NO_2$ requires 309.1729), 309 (M^+, 90%), 274 (83), 273 (85), 213 (76), 212 (100), 211 (95), 196 (89), 186 (94), 185 (87), 123 (70) and 108 (75).

2-[*N*-2-Methoxyphenylamino(phenyl)methyl]-cyclohexanone (10c)

Ivory solid; ν_{max} (KBr)/cm^{-1} 3422, 3060, 2936, 2861, 1703, 1601, 1514, 1220, 1029 and 733; δ_H (400 MHz; $CDCl_3$; Me_4Si; **A** (*syn*)/**B** (*anti*) = 40/60) 1.51–2.08 (6 H, m), 2.26–2.34 (1 H, m), 2.38–2.44 (1 H, m), 2.75–2.80 (1 H, m,), 3.83 (1.80 H, s, for **B**), 3.84 (1.20 H, s, for **A**), 4.70 (0.60 H, d, *J* 7.2, for **B**), 4.87 (0.40 H, d, *J* 3.8, for **A**), 4.96 (0.40 H, br s, for **A**), 5.12 (0.60 H, br s, for **B**), 6.39–6.44 (1 H, m), 6.55–6.60 (1 H, m), 6.63–6.73 (2 H, m), 7.15–7.19 (1 H, m), 7.24–7.29 (2 H, m) and 7.32–7.36 (2 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si; **A**/**B** = 40/60) (for **A**) 24.78, 27.05, 28.41, 42.28, 55.50, 56.31, 57.04, 109.31, 111.39, 116.61, 121.04, 126.85, 127.29, 128.29, 137.23, 141.97, 147.03 and 210.74; (for **B**) 23.61, 27.81, 30.95, 41.61, 55.48, 57.27, 57.49, 109.38, 110.86, 116.53, 120.93, 127.07, 127.29, 128.36, 137.03, 141.68, 146.99 and 212.24; *m*/*z* (EI) 309.1732

(M^+, $C_{20}H_{23}NO_2$ requires 309.1729), 309 (M^+, 77%), 213 (89), 212 (100), 196 (30), 120 (38) and 91 (27).

2-[*N*-4-Chlorophenylamino(phenyl)methyl]cyclohexanone (10d)[9g]

Light brown solid; ν_{max} (KBr)/cm^{-1} 3414, 3388, 2958, 1701, 1600, 1500, 1091, 808 and 708; δ_H (400 MHz; $CDCl_3$; Me_4Si; **A** (*syn*)/**B** (*anti*) = 32/68) 1.52–2.04 (6 H, m), 2.27–2.34 (1 H, m), 2.37–2.43 (1 H, m), 2.70–2.79 (1 H, m), 4.54 (0.68 H, d, *J* 6.9, for **B**), 4.74 (0.32 H, d, *J* 4.1, for **A**), 4.77 (1 H, s), 6.41–6.47 (2 H, m), 6.96–7.01 (2 H, m), 7.18–7.22 (1 H, m) and 7.26–7.34 (4H m); δ_C (100 MHz; $CDCl_3$; Me_4Si; **A**/**B** = 32/68) (for **A**) 24.79, 26.89, 28.39, 42.34, 56.37, 57.31, 115.15, 122.15, 127.12, 127.28, 128.41, 128.77, 140.96, 146.05 and 211.30; (for **B**) 23.78, 27.91, 31.50, 41.91, 57.31, 58.20, 114.70, 121.97, 127.16, 127.41, 128.50, 128.82, 141.20, 145.84 and 212.78; *m*/*z* (EI) 313.1221 (M^+, $C_{19}H_{20}ClNO$ requires 313.1233), 313 (M^+, 27%), 218 (75), 216 (100), 212 (46) and 138 (14).

2-[Phenyl(*N*-phenylamino)methyl]cyclopentanone (10e)[9e]

Yellow-brown solid; ν_{max} (KBr)/cm^{-1} 3381, 1727, 1604, 1513, 1153, 754 and 701; δ_H (400 MHz; $CDCl_3$; Me_4Si; **A** (*syn*)/**B** (*anti*) = 25/75) 1.63–1.79 (2 H, m), 1.83–1.93 (2 H, m), 2.04–2.16 (1 H, m), 2.22–2.35 (1 H, m), 2.46–2.52 (0.75 H, m, for **B**), 2.67–2.73 (0.25 H, m, for **A**), 4.54 (0.75 H, d, *J* 7.4, for **B**), 4.74 (0.25 H, d, *J* 4.4, for **A**), 5.17 (1 H, s), 6.52–6.66 (3 H, m), 7.03–7.08 (2 H, m) and 7.21–7.39 (5 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si; **A**/**B** = 25/75) (for **A**) 20.64, 25.84, 39.77, 53.30, 57.65, 113.62, 117.43, 127.31, 127.43, 128.51, 129.05, 140.81, 146.70 and 220.60; (for **B**) 20.45, 26.70, 39.21, 54.01, 59.01, 114.13, 117.82, 127.13, 127.39, 128.61, 128.96, 141.67, 147.49 and 219.37; *m*/*z* (EI) 265 (M^+, 53%), 183 (84), 182 (100), 180 (33), 115 (20), 104 (42), 91 (27) and 77 (61).

2-[Phenyl(*N*-phenylamino)methyl]-4-oxa-cyclohexanone (10f)

Colorless solid; ν_{max} (KBr)/cm^{-1} 3341, 3031, 2975, 2853, 1712, 1602, 1498, 1273, 1087 and 756; δ_H (400 MHz; $CDCl_3$; Me_4Si, **A** (*syn*)/**B** (*anti*) = 29/71) 2.37–2.87 (3 H, m), 3.65–4.19 (4 H, m), 4.51 (1 H, br s), 4.83 (0.71 H, d, *J* 9.3, for **B**), 4.90 (0.29 H, d, *J* 5.1, for **A**), 6.52–6.56 (2 H, m), 6.61–6.67 (1 H, m), 7.03–7.10 (2 H, m) and 7.20–7.41 (5 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si; **A**/**B** = 29/71) (for **A**) 42.24, 56.61, 57.42, 67.86, 68.61, 113.75, 117.90, 127.02, 127.47, 128.73, 129.14, 140.32, 146.68 and 207.08; (for **B**) 41.33, 56.28, 59.19, 68.53, 69.65, 113.69, 117.93, 127.27, 127.70, 128.77, 129.07, 140.54, 146.39 and 208.14; *m*/*z* (EI) 281 (M^+, 40%), 183 (65), 182 (100), 180 (33), 117 (21), 104 (33) and 77 (46).

Mixture of 1-phenyl-1-(*N*-phenylamino)-3-pentanone (10g)[7c,20] and 3-methyl-4-phenyl-4-(*N*-phenylamino)-2-butanone (10h)

Yellow solid; δ_H (400 MHz; $CDCl_3$; Me_4Si; major (**10g**)/minor (**10h**) = 53/47, **A** (*syn*-**10h**)/**B** (*anti*-**10h**) = 39/61) 0.96 (1.59 H, t, *J* 7.3, for major), 1.08 (0.54 H, d, *J* 7.0, for **A**), 1.13 (0.87 H, d, *J* 7.0, for **B**), 1.97 (0.87 H, s, for **B**), 2.09 (0.54 H, s, for **A**), 2.25–2.42 (1.06 H, m, for major), 2.89 (1.06 H, d, *J* 6.4, for major), 2.94–3.05 (0.47 H, m, for minor), 4.47 (0.29 H, d, *J* 7.2, for **B**), 4.60 (1 H, br s), 4.74 (0.18 H, d, *J* 5.4, for **A**), 4.83 (0.53 H, t, *J* 6.4, for major), 6.48–6.55 (2 H, m), 6.60–6.67 (1 H, m), 7.03–7.10 (2 H, m), 7.20–7.24 (1 H, m) and 7.28–7.36 (4 H, m); δ_C (100 MHz; $CDCl_3$; Me_4Si) 7.41, 10.98, 15.18, 29.32, 29.38, 36.90, 49.94, 53.03, 53.47, 54.52, 58.80, 60.47, 113.41, 113.57, 113.72, 117.46, 117.69, 117.75, 126.24, 126.72, 126.81, 127.32, 127.43, 128.64, 128.68, 128.77, 129.11, 140.95, 141.32, 142.59, 146.78, 146.82, 146.86, 209.91, 210.62 and 212.52.

Conclusions

We demonstrate herein the practical example of the inverse phase-transfer catalysis by acidic water-soluble calix[4]arene **1** of Mannich-type reactions in water, where it served as a recyclable catalyst. This new catalytic system requires neither co-solvents nor surfactants.

Acknowledgements

We wish to thank Nobuyuki Kobayashi and Yosuke Kobayashi for their experimental assistance. This work was financially supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology to promote advanced scientific research.

References

1 (*a*) R. T. Baker and W. Tumas, *Science*, 1999, **284**, 1477–1479; (*b*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; (*c*) J. Haggin, *Chem. Eng. News*, 1994, **72**, 16, 22–25; (*d*) E. M. Kirschner, *Chem. Eng. News*, 1994, **72**, 25, 13–20; (*e*) D. L. Illman, *Chem. Eng. News*, 1994, **72**, 36, 22–27.

2 (*a*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095–3166; (*b*) S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, 2002, **35**, 209–217; (*c*) U. K. Lindström, *Chem. Rev.*, 2002, **102**, 2751–2772; (*d*) A. Lubineau and J. Augé, Water as Solvent in Organic Synthesis, in, *Modern Solvents in Organic Synthesis*, ed. P. Knochel, Springer, Berlin, 1999, pp. 1–39; (*e*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic & Professional, London, 1998; (*f*) C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997; (*g*) J. B. F. N. Engberts, B. L. Feringa, E. Keller and S. Otto, *Recl. Trav. Chim. Pays-Bas*, 1996, **115**, 457–464; (*h*) A. Lubineau and J. Augé, Organic Chemistry in Water, in *Aqueous-Phase Organometallic Catalysis: Concepts and Applications*, ed. B. Cornils and W. A. Herrmann, Wiley-VCH, Weinheim, 1998, pp. 19–34; (*i*) W. Blokzijl and J. B. F. N. Engberts, *Structure and Reactivity in Aqueous Solution*, ed. C. J. Cramer and D. G. Truhlar, American Chemical Society, Washington DC, 1994, ch. 21, pp. 303–317; (*j*) A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 1994, 741–760; (*k*) C.-J. Li, *Chem. Rev.*, 1993, **93**, 2023–2035.

3 (*a*) S. Shimizu, K. Kito, Y. Sasaki and C. Hirai, *Chem. Commun.*, 1997, 1629–1630; (*b*) S. Shimizu, T. Suzuki, Y. Sasaki and C. Hirai, *Synlett*, 2000, 1664–1666; (*c*) S. Shimizu, S. Shirakawa, T. Suzuki and Y. Sasaki, *Tetrahedron*, 2001, **57**, 6169–6173; (*d*) S. Shimizu, T. Suzuki, S. Shirakawa, Y. Sasaki and C. Hirai, *Adv. Synth. Catal.*, 2002, **344**, 370–378.

4 For reviews, see: (*a*) Y. Goldberg, *Phase Transfer Catalysis: Selected Problems and Applications*, Gordon, Berkshire, 1992, pp. 359–366; (*b*) C. M. Starks, C. L. Liotta and M. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*, Chapman, London, 1994, pp. 179–183.

5 L. J. Mathias and R. A. Vaidya, *J. Am. Chem. Soc.*, 1986, **108**, 1093–1094.

6 (*a*) T. Akiyama, J. Takaya and H. Kagoshima, *Synlett*, 1999, 1045–1048; (*b*) T. Akiyama, J. Takaya and H. Kagoshima, *Synlett*, 1999, 1426–1428; (*c*) T. Akiyama, J. Takaya and H. Kagoshima, *Tetrahedron Lett.*, 2001, **42**, 4025–4028; (*d*) T. Akiyama, J. Takaya

and H. Kagoshima, *Adv. Synth. Catal.*, 2002, **344**, 338–347; (*e*) T. Akiyama, J. Itoh and K. Fuchibe, *Synlett*, 2002, 1269–1272.
7 (*a*) K. Manabe, Y. Mori and S. Kobayashi, *Synlett*, 1999, 1401–1402; (*b*) K. Manabe and S. Kobayashi, *Org. Lett.*, 1999, **1**, 1965–1967; (*c*) K. Manabe, Y. Mori and S. Kobayashi, *Tetrahedron*, 2001, **57**, 2537–2544.
8 For reviews on Mannich reactions, see: (*a*) E. F. Kleinman, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 2, ch 4.1; (*b*) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044–1070.
9 For Lewis acid catalysis, see: (*a*) S. Kobayashi and H. Ishitani, *J. Chem. Soc., Chem. Commun.*, 1995, 1379; (*b*) T.-P. Loh and L.-L. Wei, *Tetrahedron Lett.*, 1998, **39**, 323–326; (*c*) S. Kobayashi, T. Busujima and S. Nagayama, *Synlett*, 1999, 545–546; (*d*) T. Akiyama, J. Takaya and H. Kagoshima, *Chem. Lett.*, 1999, 947–948; (*e*) T.-P. Loh, S. B. K. W. Liung, K.-L. Tan and L.-L. Wei, *Tetrahedron*, 2000, **56**, 3227–3237; (*f*) K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 7202–7207; (*g*) B. C. Ranu, S. Samanta and S. K. Guchhait, *Tetrahedron*, 2002, **58**, 983–988; (*h*) S. Kobayashi, T. Hamada and K. Manabe, *J. Am. Chem. Soc.*, 2002, **124**, 5640–5641; (*i*) T. Hamada, K. Manabe and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 7768–7769; (*j*) T. Hamada, K. Manabe and S. Kobayashi, *Chem.–Eur. J.*, 2006, **12**, 1205–1215.
10 Most recently, Mannich-type reactions in water as the sole solvent have been reported: (*a*) S. Iimura, D. Nobutou, K. Manabe and S. Kobayashi, *Chem. Commun.*, 2003, 1644–1645; (*b*) C. Loncaric, K. Manabe and S. Kobayashi, *Adv. Synth. Catal.*, 2003, **345**, 1187–1189; (*c*) T. Akiyama, K. Matsuda and K. Fuchibe, *Synthesis*, 2005, 2606–2608.
11 For inverse phase-transfer catalysis by the water-soluble calixarene sulfonic acids, see: (*a*) E. Karakhanov, T. Buchneva, A. Maximov and M. Zavertyaeva, *J. Mol. Catal. A: Chem.*, 2002, **184**, 11–17; (*b*) A. L. Maksimov, T. S. Buchneva and E. A. Karakhanov, *J. Mol. Catal. A: Chem.*, 2004, **217**, 59–67.
12 For calixarenes bearing sulfonate and alkyl groups as surfactants for Mukaiyama aldol reactions in water, see: (*a*) H.-Y. Tian, H.-J. Li, Y.-J. Chen, D. Wang and C.-J. Li, *Ind. Eng. Chem. Res.*, 2002, **41**, 4523–4527; (*b*) H.-Y. Tian, Y.-J. Chen, D. Wang, Y.-P. Bu and C.-J. Li, *Tetrahedron Lett.*, 2001, **42**, 1803–1805; (*c*) H.-Y. Tian, Y.-J. Chen, D. Wang, C.-C. Zeng and C.-J. Li, *Tetrahedron Lett.*, 2000, **41**, 2529–2532.
13 J.-P. Scharff, M. Mahjoubi and R. Perrin, *New J. Chem.*, 1991, **15**, 883–887.
14 In contrast to the reactions using surfactants, extraction with two 10 mL-portions of ethyl acetate gave the same yield of desired product in the case of the catalyst **1**.
15 It is difficult to make a direct comparison among the yields in Entries 1–5 and Entries 6–11 (Table 2) since the corresponding reaction times are different.
16 M. Makosza, *Pure Appl. Chem.*, 1975, **43**, 439–462.
17 (*a*) C. Naumann, E. Román, C. Peinador, T. Ren, B. O. Patrick, A. E. Kaifer and J. C. Sherman, *Chem.–Eur. J.*, 2001, **7**, 1637–1645; (*b*) T. Klimova, E. Klimova, R. A. Vázquez, N. M. Gutierrez and M. Martínez, *Fullerenes Nanotubes Carbon Nanostruct.*, 2003, **11**, 269–281.
18 (*a*) S. Shimizu, S. Shirakawa, Y. Sasaki and C. Hirai, *Angew. Chem., Int. Ed.*, 2000, **39**, 1256–1259; (*b*) S. Shirakwa, S. Shimizu and Y. Sasaki, *New J. Chem.*, 2001, **25**, 777–779.
19 (*a*) D. J. Cram, S. Karbach, H.-E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson and R. C. Helgeson, *J. Am. Chem. Soc.*, 1988, **110**, 2229–2237; (*b*) E. Kh. Kazakova, N. A. Makarova, A. U. Ziganshina, L. A. Muslinkina, A. A. Muslinkin and W. D. Habicher, *Tetrahedron Lett.*, 2000, **41**, 10111–10115.
20 A. H. Blatt and N. Gross, *J. Org. Chem.*, 1964, **29**, 3306–3311.

Facile benzylation of aromatics in ionic liquid solvents promoted by TfOH, $Sc(OTf)_3$, and $Yb(OTf)_3 \cdot xH_2O$; New life for a classic transformation

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Received 2nd March 2006, Accepted 22nd May 2006
First published as an Advance Article on the web 13th June 2006
DOI: 10.1039/b603176e

Benzylation of aromatics with $PhCH_2Cl$ and $PhCH_2OH$ is conveniently performed in [BMIM][OTf] or [BMIM][PF_6] ionic liquids (ILs), by using TfOH, $Sc(OTf)_3$ and $Yb(OTf)_3 \cdot xH_2O$ as catalysts. With $PhCH_2Cl$, high conversions were achieved by using 20% $Sc(OTf)_3$ or $Yb(OTf)_3$ hydrate under mild conditions (65–80 °C). Triflic acid is superior to $Yb(OTf)_3$ as promoter for benzylation with $PhCH_2OH$ in the IL solvent, since in most cases little or no dibenzyl ether (DBE) was formed as side product. The scope of arene benzylation with benzyl alcohol in the TfOH-catalyzed and $Yb(OTf)_3$-catalyzed reactions was examined in [BMIM][PF_6] solvent. Whereas conversions are typically quantitative at 65–70 °C, minor amounts of DBE were produced, along with the corresponding $ArCH_2Ph$ (with minor amounts of dibenzylated derivatives being detected in benzylation of mesitylene and biphenyl). Substrate selectivity (K_T/K_B) and regioselectivity (isomer distribution) measured for benzylation in IL solvents employing TfOH or $Yb(OTf)_3$ as catalyst are similar to those reported previously in molecular solvents employing Nafion-H, $AlCl_3$, $TiCl_4$ or "clayzic". The observed high yields and chemoselectivities (absence of DBE), coupled to easy isolation of the benzylated products and recycling/reuse of the IL, provide a new life for this classical transformation.

Introduction

Aromatic benzylation is a synthetically important fundamental transformation for the preparation of wide variety of diarylmethanes, which are key synthetic intermediates.

In their pioneering studies focusing on the mechanistic aspects of electrophilic aromatic substitution, Olah and associates studied the $TiCl_4$-catalyzed benzylation of toluene and benzene with various substituted benzyl chlorides.[1,2] Their substrate selectivity (K_T/K_B) and regioselectivity (isomer distribution) data were consistent with a variable transition state mechanism, with "early", π-complex like, TS with destabilizing substituents, and "late", more σ-complex like, TS with stabilizing groups. Thus, electron-donating substituents in X–$PhCH_2Cl$ increased substrate selectivity (high K_T/K_B ratios) while forming comparatively more *para* isomer (lower *ortho*/*para* ratios), whereas electron-withdrawing, destabilizing substituents exhibited low substrate selectivity (smaller K_T/K_B values) and comparatively more *ortho* isomer (higher *ortho*/*para* ratios). Later, Yamato and associates[3] studied the aromatic benzylation with $PhCH_2OH$ over Nafion-H as catalyst (typically at 90–95 °C), with conversions ranging from 68–93%. In these reactions dibenzyl ether (DBE) was formed in yields ranging from 22% to 3% (see Fig. 1).

Both substrate selectivity and isomer distributions in the Nafion-H catalyzed benzylation with $PhCH_2OH$ were in close range of those measured in $PhCH_2Cl$-benzylation with $AlCl_3$ in $MeNO_2$ solvent (at 25 to >50 °C), and with the $TiCl_4$-catalyzed reaction (at 50 °C) using excess aromatics as solvent. Laszlo *et al.*[4] used K10 montmorllionite impregnated with $ZnCl_2$, "clayzic", for aromatic benzylation, by using excess arenes as solvent, with overall yields ranging from 61–97%, and with toluene/benzene selectivity in a similar range to the earlier reported values.

More recently, Latcher and associates[5] studied the efficacy of cation-exchange resins for aromatic benzylation of benzene with $PhCH_2OH$ and $PhCH_2Cl$. In these reactions, substantial amounts of DBE were isolated. Amberlyst-15 with benzyl alcohol gave the highest conversion (~99%), out of which 89% was DBE. No DBE was found in benzylation with $PhCH_2Cl$ by using other types of cation-exchange resins, but the conversions were quite low and notable amounts of dibenzylated products were also formed.

Ishii and associates[6] demonstrated the utility of metal triflates and triflic acid in secondary benzylation with benzyl alcohols Ar(Me)CHOH. The reactions were performed in $MeNO_2$, at 50–100 °C, to effect good to excellent yields, depending on the choice of substrates.

Studies focusing on the development of environmentally more acceptable processes for electrophilic aromatic benzylation have so far been quite limited.[7,8] In one case, graphite was used without employing a Lewis acid to effect benzylation of activated benzenes, namely phenol and *p*-xylene, with benzyl chloride under reflux in good yields. Under these conditions, benzene itself was not benzylated. Moreover, the use of excess arene was required to avoid competing di- and poly-benzylation.[7] In the second study,[8] benzylation of benzene with $PhCH_2Cl$ was performed in [BMIM][Cl]/$AlCl_3$ ionic liquids. Optimum conversions and selectivity were observed with

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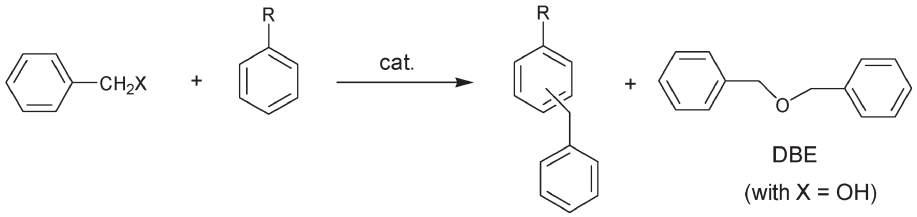

Fig. 1 Benzylation reaction of aromatics.

[BMIM][Cl]/$AlCl_3$ = 1 : 2, and by using a large excess of the arene. The chloroaluminate IL, however, exhibited limited lifetime, and a sudden drop in conversion and selectivity were reported following two successful runs.

In continuation of our previous studies focusing on electrophilic chemistry in ionic liquids,[9–13] and in an effort to improve on the existing methods for aromatic benzylation, we report here our survey study of arene benzylation with $PhCH_2Cl$ and $PhCH_2OH$, employing TfOH, $Sc(OTf)_3$ and $Yb(OTf)_3{\cdot}xH_2O$ as promoters.

Results and discussion

At the onset, benzylation of toluene and anisole with $PhCH_2Cl$ was studied in [BMIM][OTf] ionic liquid by using $Sc(OTf)_3$ and $Yb(OTf)_3$ hydrate as catalyst. The results are summarized in Table 1. The $Sc(OTf)_3$-catalyzed benzylation of toluene gave an 18% conversion after 20 h stirring at r.t. In a subsequent run, employing recycled IL, a 96% conversion was obtained after 20 h at 65 °C. Shorter reaction times led to lower conversions (run 3). A 96% conversion was achieved in benzylation of anisole after 6 h stirring at 80 °C, with slightly lower conversions being observed at lower temperatures and with shorter reaction times. Conversions in the 90–100% range were achieved in the $Yb(OTf)_3$ hydrate catalyzed benzylations at 65–80 °C. The $PhCH_2Cl$:ArH:catalyst molar ratios were typically 1.0 : 4.0 : 0.2. The isomer distribution in benzylation of toluene with either $Sc(OTf)_3$ or $Yb(OTf)_3$ were close to the earlier reported values with other catalysts.

In the next phase of this study, benzylation of benzene, toluene and anisole with $PhCH_2OH$ was performed in TfOH, and in $Yb(OTf)_3{\cdot}xH_2O$ as catalysts. The data are summarized in Table 2. It can be seen that benzene is efficiently benzylated to diphenylmethane in both TfOH and $Yb(OTf)_3$. These reactions were carried out at 65 °C for 20 h. Although conversion based on $PhCH_2OH$ was quantitative in both systems, benzylation with TfOH exhibited higher chemoselectivity to the formation of diphenylmethane, giving rise to only 19% DBE. These findings show that the herein described systems are superior to the earlier reported benzylations with Nafion-H and with cation exchange resins in terms of both overall conversion and chemoselectivity. By comparing the data for benzylation of toluene and anisole with $PhCH_2OH$, it can be seen that although quantitative conversions could be achieved with both catalyst systems, rather significant amounts of DBE were present with $Yb(OTf)_3$ hydrate. An inverse relationship is observed between the %DBE present in the $Yb(OTf)_3$-catalyzed reaction of toluene and the reaction temperature. This suggests that formation of the benzylation electrophile is less efficient at r.t., thus promoting *o*-benzylation of the alcohol precursor. By contrast, no DBE was detected in the TfOH-catalyzed reactions, indicating that benzyl alcohol is efficiently protonated by TfOH. However, since the progress of the reaction was not monitored at intervals, it is not possible to rule out protonated DBE as a contributing benzylating agent.

There are no significant variations in the isomer distributions in these systems, with the *para* isomer being slightly favored over *ortho* (for both toluene and anisole), and the *meta* remaining very low in all cases (in some cases not even detectable).

For the TfOH catalyzed benzylation of toluene, typically 0.5 equivalents of TfOH at 60 °C constituted optimal conditions for quantitative conversion, whereas with anisole 0.25 equivalents of TfOH at 65 °C was optimal. Furthermore, no noticeable drop in the conversions was observed when using recycled/re-used IL in 3–4 consecutive runs.

Table 1 Benzylation of toluene and anisole with $PhCH_2Cl$ in [BMIM][OTf][a]

ArH	Catalyst	$PhCH_2Cl$:ArH:cat. molar ratio	Reaction time/h	Temp./°C	Conv.(%)	Isomer distribution		
						o- (%)	*m*- (%)	*p*- (%)
Toluene	$Sc(OTf)_3$	1 : 6 : 0.2	20	25	18	42	nd	58
		1 : 4 : 0.2	20	65	96	43	nd	57
		1 : 4 : 0.2	4	65	77	43	nd	57
Anisole	$Sc(OTf)_3$	1 : 4 : 0.2	20	65	74	45.5	0.5	54
		1 : 4 : 0.2	6	80	95	47	1.0	52
		1 : 4 : 0.2	20	25	21	43	0.5	57.5
Toluene	$Yb(OTf)_3$	1 : 4 : 0.2	16	70	90	42	nd	58
		1 : 4 : 1.0	20	80	100	41	nd	59
Anisole	$Yb(OTf)_3$	1 : 4 : 0.2	20	65	91	43	nd	57
		1 : 20 : 1.0	4	80	100	45	nd	55

[a] For each group of reactions fresh IL was employed in the first run and used/recycled IL was utilized in subsequent experiments; nd = not detectable.

Table 2 Benzylation of aromatics with $PhCH_2OH$ in [BMIM][OTf][a]

ArH	Catalyst	$PhCH_2OH$:ArH:cat. (molar ratio)	Reaction time/h	Temp./°C	Total conversion[b] (%)	Composition of reaction mixture			
						$(Ph)_2CH_2$ (%)			DBE[c] (%)
						$ArCH_2Ph$ Isomer Distribution			
						***o*- (%)**	***m*- (%)**	***p*- (%)**	
Benzene	$Yb(OTf)_3$	1 : 4 : 0.5	20	65	100	62			38
	TfOH	1 : 4 : 0.2	20	65	100	83			19
Toluene	$Yb(OTf)_3$	1 : 2 : 0.5	48	25	97	36	6.5	57.5	44.5
		1 : 4 : 0.5	16	65	90	40	5.0	55	35
		1 : 8 : 0.5	20	65	97	39.5	5.5	55	32
		1 : 4 : 0.6	20	65	100	40	5.0	55	29
		1 : 4 : 0.3	20	80	100	41.5	5.5	53	26
Toluene	TfOH	1 : 2 : 0.5	20	60	100	39.5	5.0	55.5	—
		1 : 8 : 1.0	20	60	100	42	2.0	56	—
		1 : 4 : 1.0	20	60	100	41.5	3.0	55.5	—
Anisole	$Yb(OTf)_3$	1 : 4 : 0.2	3	65	100	49	nd	51	28
		1 : 4 : 0.3	3	65	100	43	nd	57	29
		1 : 20 : 1.0	4	70	100	45	nd	55	12
Anisole	TfOH	1 : 4 : 0.25	20	65	100	40.5	nd	59.5	—
		1 : 8 : 1.0	16	65	100	43	nd	57	—
		1 : 2 : 0.5	3	65	100	43	nd	57	—
		1 : 30 : 1.0	3	65	100	43	nd	57	—

[a] for each group of reactions, fresh IL was employed in the first run and used/recycled IL was utilized in subsequent experiments; nd = not detected. [b] $ArCH_2Ph$ isomers plus DBE if formed. [c] DBE = dibenzyl ether.

The scope of the TfOH-catalyzed benzylation of various substituted benzenes (isomeric xylenes, ethylbenzene, mesitylene, 1,2,4-trimethylbenzene and biphenyl) was then examined using $PhCH_2OH$ in [BMIM][PF_6] ionic liquid. The data are summarized in Table 3. Whereas isomer distribution in the TfOH-catalyzed benzylations of EtPh and MePh are very similar, DBE was found as a byproduct in the case of EtPh. By using 0.2 equivalents of TfOH, after 3 h at 70 °C 10% DBE was present, whereas 24% DBE was present in the reaction that employed less TfOH (0.1 equiv.) and had a shorter reaction time. These findings re-enforce the hypothesis that DBE originates from a less complete protonation of benzyl alcohol and that it could be a competing benzylating agent.

Table 4 summarizes the results of the same survey study using $Yb(OTf)_3$ hydrate as promoter in [BMIM][PF_6] as solvent. Under these conditions quantitative conversions were reached in all cases, except for biphenyl. Therefore, both catalyst systems are efficient for arene benzylation in ILs, but presence of DBE (albeit in minor quantities in many instances) occurs more generally in the case of $Yb(OTf)_3$ hydrate with minor amounts of di-benzylation with biphenyl.

In the ethylbenzene reaction in TfOH, a trace of the *meta* isomer (~3%) could be detected in the GC, but no separate peak due to the *meta* isomer could be seen in the GC of the $Yb(OTf)_3$ hydrate reaction (Tables 3 and 4). In order to explore if the *meta*-benzyl isomer could be increased in the mixture by subsequent isomerization of the *ortho*/*para* isomers, in a control experiment the isomeric mixture obtained from the $Yb(OTf)_3$ hydate reaction was treated with TfOH in [BMIM][PF_6] under the benzylation reaction conditions. GC analysis of the reaction mixture following isolation indicated <3% *meta*, therefore an intermolecular process (debenzylation/rebenzylation) is not favorable. It is well established that in benzylation of toluene the *meta* isomer always remains low, irrespective of the nature of the electrophile or the catalyst.[1–3] Similar findings were reported previously in benzylation of

Table 3 TfOH-catalyzed benzylation of aromatics with $PhCH_2OH$ in [BMIM][PF_6][a]

ArH	$PhCH_2OH$:ArH:TfOH (molar ratio)	Reaction time/h	Temp./°C	Total conversion[b] (%)	Composition of reaction mixture				
					I[c]	II[c]	III[c]	DBE[d]	other[d]
					Isomer distribution (%)				
ortho-Xylene	1 : 4 : 0.5	20	70	100	100	—	—	—	—
meta-Xylene	1 : 4 : 0.5	20	70	100	20.5	79.5	—	—	—
para-Xylene	1 : 4 : 0.5	20	70	100	100	—	—	—	—
	1 : 8 : 0.2	6	65	100	100	—	—	—	—
EtC_6H_5	1 : 8 : 0.2	3	65	100	40 (*ortho*)	3.0 (*meta*)	57.0 (*para*)	10	—
	1 : 8 : 0.1	1.5	65	96	41.5 (*ortho*)	3.5 (*meta*)	55.0 (*para*)	24	—
Mesitylene	1 : 4 : 0.5	20	70	100	96	—	—	4.0	—
	1 : 4 : 1.0	20	70	100	98	—	—	2.0	—
1,2,4-$Me_3C_6H_3$	1 : 4 : 0.1	3 days	50	100	0.5	49	50.5	8.0	—
	1 : 4 : 0.2	20	70	100	0.5	42.5	57	—	6.0
Biphenyl	1 : 4 : 0.5	68	70	92	63	37	—	—	7.0

[a] For each group of reactions, fresh IL was employed in the first run and used/recycled IL was employed in subsequent experiments. [b] Isomeric benzylated arene plus DBE, plus other (if applicable). [c] I, II, III – corresponding $ArCH_2Ph$ isomers in order of increasing retention time (see text). [d] DBE = dibenzyl ether; other = dibenzylated arene.

Table 4 $Yb(OTf)_3$ hydrate-catalyzed benzylation of aromatics with $PhCH_2OH$ in $[BMIM][PF_6]$[a]

ArH	$PhCH_2OH$:ArH:TfOH (molar ratio)	Reaction time/h	Temp./°C	Total conversion[b] (%)	Composition of reaction mixture: I[c] Isomer distribution (%)	II[c]	III[c]	DBE[d]	other[d]
ortho-Xylene	1 : 4 : 0.5	48	70	100	100	—	—	—	—
meta-Xylene	1 : 4 : 0.5	20	65	100	—	94	—	6	—
para-Xylene	1 : 4 : 0.5	20	70	100	100	—	—	—	—
	1 : 4 : 1.0	20	70	100	100	—	—	—	—
EtC_6H_5	1 : 8 : 0.2	3	65	100	44	—	56	2	—
	1 : 8 : 0.2	1.5	65	100	44	—	56	21	—
Mesitylene	1 : 4 : 0.5	20	70	100	100	—	—	9	—
	1 : 4 : 1.0	20	70	100	100	—	—	8	—
	1 : 4 : 0.1	20	65	100	100	—	—	4	—
	1 : 8 : 0.2	6	65	100	100	—	—	2	—
$1,2,4\text{-}Me_3C_6H_3$	1 : 4 : 0.1	20	60	100	0.5	43.5	56	2	—
	1 : 4 : 0.2	20	60	100	0.5	44.5	55	6.0	—
Biphenyl	1 : 4 : 0.5	20	70	80	56	44	—	—	19

[a] For each group of reactions, fresh IL was employed in the first run and used/recycled IL was employed in subsequent experiments. [b] Isomeric benzylated arene plus DBE, plus other (if applicable). [c] I, II, III – corresponding $ArCH_2Ph$ isomers in order of increasing retention time (see text). [d] DBE = dibenzyl ether; other = dibenzylated arene.

anisole using *in-situ* generated benzyl triflate,[14] and are seen in the present study employing $Sc(OTf)_3$, $Yb(OTf)_3$ hydate and TfOH in ionic liquid solvents. Therefore, formation of the *meta*-benzyl isomer in benzylation of toluene, ethylbenzene and anisole is unfavorable both intramolecularly (isomerization within the arenium ion) and intermolecularly (*via* debenzylation/rebenzylation). The only previously studied exception was 2,6-dimethylanisole which gave significant amounts of *meta* isomer. However, it was shown that in this case the *meta* isomer resulted from initial *o*-benzylation followed by benzyl-shift *via* an intramolecular process.[14]

With *o*-xylene, a single benzylated isomer (the 4-benzyl derivative) was formed with both catalysts, but with *m*-xylene, there were two benzylated isomers (the 2-benzyl- and 4-benzyl-derivatives, with the 4-isomer being major). Both catalysts systems proved efficient for benzylation of mesitylene in the IL solvent (with conversions ranging from 96–100%), with little DBE (<10%) being formed in all cases. Benzylation of 1,2,4-trimethylbenzne resulted in 2 major isomers (3-benzyl- and 5-benzyl-derivatives) and tiny amounts of another isomer (6-benzyl-derivative), with very little DBE being detected at the end of the reactions. Finally with biphenyl, two isomeric monobenzylated derivatives (4-benzyl- and 2-benzyl-), along with small amounts of the dibenzylated products, were formed.

In an effort to shed some light on the nature of the benzylation electrophile in the IL solvent, and for comparison with the previously reported selectivities in molecular solvents, substrate selectivity (K_T/K_B) in benzylation with $PhCH_2OH$ promoted by TfOH was measured in [BMIM][OTf]. Substrate selectivity was also determined for $Yb(OTf)_3$ hydrate-catalyzed reactions, with both [BMIM][OTf] and $[BMIM][PF_6]$ as solvents. The data are summarized in Table 5, along with the earlier reported data under various conditions. The K_T/K_B values measured in the IL solvents for the two benzylation systems are in the range of the previous values, as are the *ortho*/*para* ratios (positional selectivities), indicating that the nature of the benzylation electrophile is not affected to any notable extent in the ionic liquid solvent. The change in substrate selectivity between [BMIM][OTf] and $[BMIM][PF_6]$ for the $Yb(OTf)_3$ hydrate catalyzed competitive reaction is rather small (an added complication with $[BMIM][PF_6]$ is the possibility of competing anion exchange with the catalyst system). Therefore, no clear changes reflecting differing solvation effects due to the IL are noted. The observed low K_T/K_B values are compatible with the formation of a reactive electrophile and a relatively early transition state. By comparison, electrophilic admantylation[13] and fluorination[11] of arenes exhibited slightly higher substrate selectivities in the IL solvents as compared to MeCN, implying a comparatively later transition state in the IL (increased carbocationic character). In contrast, solvolysis of Ar_2CHCl in TFE indicated a shorter lifetime for the carbenium ion in the IL relative to MeCN, which was suggested to be due to increased electrophilicity of the carbenium ion.[15] Taken together, these studies point to variable life-times for the carbocationic intermediates in the IL solvents relative to molecular solvents, depending on the nature of the transformation, structures of the electrophile and intermediate, solvation effects and nature

Table 5 Competitive benzylation of benzene–toluene (1 : 1) in the presence of various catalysts

Catalyst	$PhCH_2X$	Solvent	Temp./°C	K_T/K_B	*ortho*	*meta*	*para*	*o*-/*p*-	Ref.
TfOH	$C_6H_5CH_2OH$	IL[a]	65	4.8	40.3	5.1	54.6	0.37	this work
$Yb(OTf)_3$		IL[a]	65	5.8	40.0	5.5	54.5	0.37	this work
$Yb(OTf)_3$		IL[b]	65	3.5	44.0	4.8	51.2	0.43	this work
Nafion-H		Arene[c]	90	3.6	41.9	2.8	55.3	0.38	3
$TiCl_4$	$C_6H_5CH_2Cl$	Arene[c]	50	6.0	41.0	4.5	54.5	0.38	1,2
Clayzic[d]		Arene[c]	40	4.7	—	—	—	—	4

[a] IL = [BMIM][OTf]. [b] IL = $[BMIM][PF_6]$. [c] Benzene–toluene. [d] Montmorillonite K-10 impregnated with zinc chloride.

of the ionic liquid, in particular the size and nucleophilicity of its counterion. Further studies to examine these variables are of great interest.

In summary, the present survey study shows that benzylation of aromatics can be conveniently carried out in imidazolium ILs. Conversions are usually excellent and little or no DBE is detected at the end of the reactions. The process could be repeated with recycled/reused IL without any noticeable decrease in the conversions. Substrate and positional selectivities in competitive reactions were found to be similar to the previously reported systems in molecular solvents.

Experimental

General

All items of glassware were oven-dried at 120 °C and flushed with nitrogen prior to use. Benzylation reactions were carried out in small Schlenk tubes under nitrogen. Reagents were transferred and manipulated under dry nitrogen.

Benzyl chloride and benzyl alcohol were high purity commercial samples (Aldrich), which were used without further purification. The [BMIM][OTf] and [BMIM][PF_6] ionic liquids were purchased from ACROS and from Merck, and used without any pre-treatment. The aromatic compounds were highest purity commercial samples, and purities were checked by GC prior to use. $Sc(OTf)_3$ was purchased from Aldrich and was handled under nitrogen. $Yb(OTf)_3 \cdot xH_2O$ (Aldrich) was available from previous studies.

Triflic acid (Aldrich) was stored under nitrogen in a Nalgene bottle in a freezer. Anhydrous Et_2O was used for extraction.

Typical procedure

The [BMIM][OTf] ionic liquid (1.15 g, 4.43 mmol) was charged into a Schlenk tube and $PhCH_2OH$ (0.108 g, 1 mmol) was added under nitrogen. The closed Schlenk tube was placed in an ultrasonic bath at r.t. for several minutes (typically 10–15 min) to increase miscibility. After addition of anisole (0.432, 4.0 mmol) under nitrogen and magnetic stirring at r.t. for 10 min, the Schlenk tube was cooled to 0 °C and TfOH (0.05 mL, 0.5 mmol) was added under nitrogen *via* a micropipette. The Schlenk tube was re-sealed and placed in a thermostatic bath at 65 °C, under magnetic stirring, for 3 h. Typical work-up procedure involved addition of dry Et_2O (4 mL × 5) and neutralization of combined extracts (as a precaution for subsequent GC-MS analysis) by washing with water (4 mL × 2), with 5% $NaHCO_3$ (4 mL × 2) and water (4 mL × 2) consecutively, followed by separation of the organic phase, drying ($MgSO_4$) and simple filtration. The procedure was similar for $C_6H_5CH_2Cl$ with $Yb(OTf)_3$ hydrate and $Sc(OTf)_3$. In the latter case, the reactions were carried out at 80 °C. In competitive experiments great care was taken to prepare and transfer the benzene/toluene equimolar mixtures as carefully as possible. For $Sc(OTf)_3$-catalyzed reactions, the Lewis acid catalyst was immobilized in the IL by sonication. Following the general procedure outlined above, the reactions were conducted at 80 °C overnight to increase conversion.

Reaction mixtures were analyzed by a SATURN 2100D GC/MS/MS instrument utilizing a Chrompack capillary column (CP-SII 8 CB Low Bleed/MS 30 m, 0.25 mm 0.25 im #CP 5860), programmed from 34 °C to 250 °C, with He($\sim$2 mL min^{-1}) as carrier gas. Conversions were determined by GC and are based on $PhCH_2$-X. Subsequent vacuum drying of the reaction mixtures left behind the benzyl-aromatics, which were re-examined by GC-MS analysis. The DBE and dibenzylated arenes (if present) were separated from $ArCH_2Ph$ by preparative TLC (hexane/ethyl acetate = 10 : 1), or by column chromatography and the monobenzylated products were directly assayed by ^1H NMR, and in selected cases by ^{13}C NMR. The benzylated products obtained in this study were all known compounds and their physical and analytical data had previously been reported.[16–21]

Diphenylmethane. MS: 167 (100, $M-1^+$), 152 (30), 115 (10), 91 (20), 65 (15), 51 (20).

1-Methyl-4-(phenylmethyl)-benzene. MS: 182 (75, M^+), 167 (100), 104 (40), 65 (30), 50 (30);

1-Ethyl-4-(phenylmethyl)-benzene. MS: 196 (100, M^+), 181 (25), 167 (95), 152 (20), 118 (65), 91 (25), 77 (15), 51 (15).

1,2-Dimethyl-3-(phenylmethyl)-benzene. MS: 196 (65, M^+), 181 (100), 166 (45), 115 (15), 91 (25), 77 (20), 51 (20);

1,3-Dimethyl-2-(phenylmethyl)-benzene. MS: 196 (69, M^+), 181 (100), 166 (45), 118 (20), 91 (25), 77 (25), 51 (25);

1,4-Dimethyl-2-(phenylmethyl)-benzene. MS: 196 (90, M^+), 181 (100), 165 (45), 152 (10), 117 (30), 91 (25), 77 (20), 51 (25);

1,3,5-trimethyl-2-(phenylmethyl)-benzene. MS: 210 (100, M^+), 195 (100), 180 (50), 165 (35), 152 (10), 133 (25), 117 (30), 91 (45), 77 (30), 51 (35);

1,2,4-trimethyl-5-(phenylmethyl)-benzene. MS: 210 (80, M^+), 195 (100), 180 (30), 165 (35), 91 (30), 51 (25)

4-benzylbiphenyl. MS: 244 (100, M^+), 229 (15), 215 (10), 202 (5), 165 (60), 91 (5), 78 (15), 51 (15).

Recycling of the Ionic Liquid

Following the removal of organics from the IL phase by Et_2O extraction, the used IL was heated in the same Schlenk tube under high vacuum at 100 °C for several hours or overnight to remove any residual organics. The recovered [BMIM][OTf] was used numerous times (typically 3–5 runs) without compromising the efficiency of the benzylation reactions.

Acknowledgements

V. D. S. thanks Prof. J. Mague for financial support and for the opportunity to conduct part of this work at Tulane (in Prof. C.-J. Li's lab). The authors also thank Dr J. E. Bollinger and Dr L. Chen (both at Tulane) for their technical assistance.

References

1 G. A. Olah, M. Tashiro and S. Kobayashi, *J. Am. Chem. Soc.*, 1970, **92**, 6369.
2 G. A. Olah, *Friedel–Crafts Chemistry*, Wiley, New York, 1973, pp. 504–505.
3 T. Yamato, C. Hideshima, G. K. S. Prakash and G. A. Olah, *J. Org. Chem.*, 1991, **56**, 2089.
4 A. Cornelis, C. Dony, P. Laszlo and K. M. Nsunda, *Tetrahedron Lett.*, 1991, **32**, 1423.
5 M. S. M. da Silva, C. L. Da Costa, M. De Magdala Pinto and E. R. Lachter, *React. Polym.*, 1995, **25**, 55.
6 M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima and K. Ishi, *J. Org. Chem.*, 2003, **68**, 9340.
7 G. A. Sereda, *Tetrahedron Lett.*, 2004, **45**, 7265.
8 D.-S. Kim and W.-S. Ahn, *Korean. J. Chem. Eng.*, 2003, **20**, 39.
9 K. K. Laali and V. J. Gettwert, *J. Org. Chem.*, 2001, **66**, 35.
10 K. K. Laali and V. J. Gettwert, *J. Fluorine Chem.*, 2001, **107**, 31.
11 K. K. Laali and G. I. Borodkin, *J. Chem. Soc., Perkin Trans. 2*, 2002, 953.
12 V. D. Sarca and K. K. Laali, *Green Chem.*, 2004, **6**, 245.
13 K. K. Laali, V. D. Sarca, T. Okazaki, A. Brock and P. Der, *Org. Biomol. Chem.*, 2005, **3**, 1034.
14 K. Laali, *J. Org. Chem.*, 1985, **50**, 3638.
15 R. Bini, C. Chiappe, D. Pieraccini, P. Piccioli and C. S. Pomelli, *Tetrahedron Lett.*, 2005, **46**, 6675.
16 T. Kondo, S. Kajiya, S. Tantayanon and Y. Watanabe, *J. Organomet. Chem.*, 1995, **489**, 83.
17 N. N. Karade, S. G. Shirodkar and R. A. Potrekar, *J. Chem. Res.*, 2003, 652.
18 A. Flaherty, A. Trunkfield and W. Barton, *Org. Lett.*, 2005, **7**, 4975.
19 R. W. Darbeau, E. H. White, F. Song, N. R. Darbeau and J. Chou, *J. Org. Chem.*, 1999, **64**, 5966.
20 I. V. Kozhevnikov, V. I. Kim, E. P. Talzi and V. N. Sidelnikov, *J. Chem. Soc., Chem. Commun.*, 1985, 1392.
21 Yu. V. Pozdnyakovich, V. V. Borodovitsyn, S. A. Pozdnyakovich and S. M. Shein, *Zh. Org. Khim.*, 1983, **19**, 403.

Anion effects on the cytotoxicity of ionic liquids†

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Received 13th February 2006, Accepted 22nd May 2006
First published as an Advance Article on the web 15th June 2006
DOI: 10.1039/b602161a

Most recent investigations concerning the toxicological and ecotoxicological risk potentials of ionic liquids are predominantly focusing on the cation moieties. In this study we elucidate, whether the anion species commonly used in ionic liquids are exhibiting intrinsic cytotoxic effects and if these effects can be rationalised by thinking in terms of structure–activity relationships (T-SAR). As test system to measure the cell viability as toxicologically relevant endpoint the IPC-81 rat leukemia cell line and the WST-1 assay were employed. Our results show an anion effect in ionic liquids on cytotoxicity for 10 of 27 tested anions. For the remaining 17 anions from our test kit no significant effect was found. With respect to structure–activity relationships, lipophilicity and/or vulnerability to hydrolytic cleavage seem to be the key structural features leading to the observed anion cytotoxicity. We also conclude that the model of concentration addition may be useful to estimate the EC_{50} values of ionic liquids that have not been tested or even synthesised yet. This can help to design not only task specific but also inherently safer ionic liquids.

Introduction

Ionic liquids are a fascinating group of chemicals that have found manifold applications, *e.g.* in organic synthesis,[1] catalysis,[2] biocatalysis,[3] and electrochemistry.[4] Main advantages of ionic liquids as compared to common molecular organic solvents are their negligible vapour pressure, resulting in reduced inhalatory exposure and absence of flammability, and their high variability concerning chemical structure of headgroups, substituents and anions. These variabilities and combinations thereof lead to an enormous number of theoretically accessible ionic liquids.[5] The possibility to modify structural elements in order to optimise technological features like solvation properties, viscosity, conductivity and thermal as well as electrochemical stability is ideal in terms of technical applicability. Thus, ionic liquids can be tailored and tuned.[6] However, concerning the risk assessment for man and the environment this structural variability presents an almost insurmountable problem as it is impossible to generate profound knowledge of the effects on human health and the environment for every single compound in this heterogeneous substance group.

This dilemma on the one hand originates from preparative creativity that yields more and more new chemical structures with properties of an ionic liquid and on the other hand from the enormous efforts that would be required to accurately test their effects in biological systems with different levels of complexity. To overcome this problem, we have proposed an approach that allows to investigate the (eco)toxicity of individual structural elements (toxicophore/ecotoxicophore) of ionic liquids. These elements can be roughly classified as headgroup, side chain and anion.[7] To generate knowledge on how these individual structural variables may evoke effects on molecules of life, cells, and organisms, we have developed an approach to systematically select and analyse them according to the T-SAR concept (thinking in terms of structure–activity relationships).[7–9] The different structural elements are combined based on our test kit concept[7,10] in a set of ionic liquids in which only one parameter (*e.g.* side chain length) is changed.

Following this strategy, so far we have concentrated on analysing the effects of the alkyl side chain length of various headgroups (*e.g.* methylimidazolium, pyridinium *etc.*) as well as the influence of the headgroups in biological systems of different complexity. A side chain length effect was discovered from the molecular (acetylcholinesterase)[11] up to organism level (plants).[7] This side chain effect has been shown in many other studies focused on the identification of the hazard potential of ionic liquids for man and the environment.[12–19] In our recent paper we could show that the influence of the headgroup on cytotoxicity is mainly driven by the lipophilicity of the compound.[20]

Beside the cationic headgroup of ionic liquids, the anion plays a central role as technicophore, because it exhibits a high potential for tuning technological properties (*e.g.* solubility, viscosity *etc.*). Therefore the key question of this study was, whether the anion as toxicophore/ecotoxicophore of an ionic liquid can influence biological effects. So far, the anions investigated in literature generally showed no significant effects.[12–20]

For our investigations, we used the promyelotic leukemia rat cell line IPC-81[21] as test system with the enzymatic reduction of the WST-1[22,23] dye as an indicator of cell viability.

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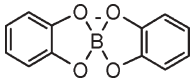
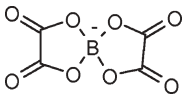
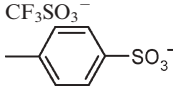
† Electronic supplementary information (ESI) available: Confidence intervals and a complete listing of the parameters of the fitted models. See DOI: 10.1039/b602161a

Table 1 Formulas and structures of all investigated anions (anion test kit)

No.	Structure	Name	No.	Structure	Name
1	BF_4^-	Tetrafluoroborate	13	SCN^-	Thiocyanate
2		Bis-[1,2-benzenediolato (2-)] borate (BBDB)	14	HSO_4^-	Hydrogen sulfate
			15	$CH_3OSO_3^-$	Methyl sulfate
			16	$C_2H5OSO_3^-$	Ethyl sulfate
3		Bis-[oxalato(2-)]-borate (BOB)	17	$C_8H_{17}OSO_3^-$	Octyl sulfate
			18	$H_3CO(CH_2)_2O–(CH_2)_2OSO_3^-$	2-(2-Methoxyethoxy)ethylsulfate
			19	$H_3C–(O–CH_2–CH_2)_nOSO_3^-$	Methyl-poly(oxy-1,2-ethanediyl) sulfate
			20	$CH_3SO_3^-$	Methanesulfonate
4	$(CF_3SO_2)_3C^-$	Tris(trifluoromethylsulfonyl)methide	21	$CF_3SO_3^-$	Trifluoromethanesulfonate
5	$(CN)_2N^-$	Dicyanamide	22		Tosylate (Tos)
6	$N(CF_3)_2^-$	Bis(trifluoromethyl)imide			
7	$N(SO_2CF_3)_2^-$	Bis(trifluoromethylsulfonyl)imide	23	F^-	Fluoride
8	PF_6^-	Hexafluorophosphate	24	Cl^-	Chloride
9	$(C_2F_5)_3PF_3^-$	Tris(pentafluoroethyl)trifluorophosphate	25	Br^-	Bromide
10	$(C_3F_7)_3PF_3^-$	Tris(heptafluoropropyl)trifluorophosphate	26	I^-	Iodide
11	$[(C_2F_5)_2P(O)O^-$	Bis(pentafluoroethyl)phosphinate	27	$Co(CO)_4^-$	Cobalttetracarbonyl
12	SbF_6^-	Hexafluoroantimonate			

We concentrated on the question, whether the anion is cytotoxic just by itself or exhibits a modified cytotoxicity by the combination with certain cations *e.g.* by forming an ion pair. Thus, we address the problem, whether or not ionic liquids cytotoxicity also has to be considered in terms of mixture toxicity. Published studies investigating this additional issue are still missing.

The results presented here for 27 different anions highlight that cytotoxicological effects of certain ionic liquids can be found depending on the chemical structure of the anion. Hence, the postulation of an anion effect is justified.

Furthermore, we could show that in fact certain anions can modify the intrinsic cytotoxicity of a cation leading to some type of mixture toxicity. In contrast, most of the investigated anions resulted in a similar cytotoxicity as compared to chloride as reference anion indicating no additional mixture toxicity or specific anion effect.

Considering these facts, our data open up the possibility to systematically vary the anion for reaching the goal of sustainable design of task specific ionic liquids as the anion constitutes an important factor not only for the improvement of the technical features of ionic liquids but also for reducing their risk to man and the environment.

Results

Selection of the test kit compounds

Looking at the commercially available anions used in ionic liquids a high diversity of structures is encountered.[7] We organised them according to the central atom that forms the anion as well as on the basis of the structures that are aligned sorted by the periodic table (Table 1).

To analyse the intrinsic cytotoxicity of the anion, we combined anions with either the sodium or the lithium cation depending on their availability. In our test system sodium chloride as well as lithium chloride showed no cytotoxic effects up to the highest tested concentration (5 mM).

To reduce the structural variety and thus to increase the interpretability of our results, we concentrated on the 1-alkyl-3-methyl-imidazolium headgroup with three different side chain lengths (Fig. 1). The test matrix consisted of a total of 53 substances, including 35 ionic liquids. For all compounds listed the cytotoxicity, expressed in EC_{50} values was tested in the WST-1 cell viability assay using the IPC-81 cell line (Table 2). This test system is well established in our laboratory and has proven to provide reproducible results for measuring cytotoxicity of various industrial chemicals.[8,14,24,25] Confidence intervals and a complete listing of the parameters of the fitted models are given in the Electronic Supplementary Information, ESI.†

Cytotoxicity of alkali salts

Neither NaCl nor LiCl showed cytotoxicity in the tested concentration range up to 5 mM. Therefore, it was concluded that neither the sodium nor the lithium cation exhibits an intrinsic cation effect, and further, that the chloride anion does not exhibit an intrinsic anion effect. Taking a closer look at the anions showing cytotoxicity, the following features can be identified. Among the halogen ions (no. 23 to 26) only the fluoride ion is active within the tested concentration range with an EC_{50} value around 1200 μM. A relatively high cytotoxicity was found for the sodium salt of the SbF_6 anion (no. 12). In particular the boron containing anions bis-[1,2-benzenediolato(2-)] borate (BBDB) and bis-[oxalato(2-)]-borate (BOB)

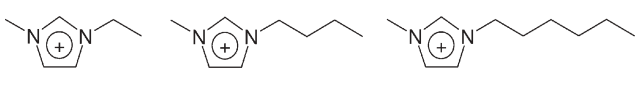


Fig. 1 Cation test kit. The presented 1-alkyl-3-methylimidazolium headgroups with different chain lengths at the 1-position constitute the core cationic structures of our test kit. Additionally lithium and sodium cations were used as counterions for the anion tests.

Table 2 Cytotoxicities of all investigated salts expressed as EC_{50} values. The cytotoxicity of the chlorides (line 24, italic) are taken as reference values, for which anion cytotoxicity is assumed to be zero. The 1-alkyl-3-methylimidazolium cations are abbreviated according to their alkyl chain length with C_2MIM, C_4MIM and C_6MIM. For ionic liquids containing the anions no. 4, 9 and 10 the EC_{50} values can only be estimated due to the low solubility of these compounds. Therefore the corresponding EC_{50} values are listed with "<" because the real test concentration of the substances is assumed to be lower than the nominal one

		EC_{50} values/μM				
No.	Anion	Na^+	Li^+	C_2MIM	C_4MIM	C_6MIM
1	BF_4^-	>4000		3400	1700	960
2	$BBDB^-$		13	10		
3	BOB^-		760	860		
4	$(CF_3SO_2)_3C^-$					<100
5	$(CN)_2N^-$	14000			1400	
6	$N(CF_3)_2^-$				150	
7	$N(SO_2CF_3)_2^-$		2200		480	180
8	PF_6^-			8400	1300	810
9	$(C_2F_5)_3PF_3^-$			<100	<100	<100
10	$(C_3F_7)_3PF_3^-$					<50
11	$(C_2F_5)_2P(O)O^-$			680		
12	SbF_6^-	200			180	
13	SCN^-	>20000			2600	
14	HSO_4^-	7800			1900	
15	$CH_3OSO_3^-$	>10000			1700	
16	$C_2H_5OSO_3^-$			8500		
17	$C_8H_{17}OSO_3^-$	3000			1700	
18	$H_3CO(CH_2)_2O–(CH_2)_2OSO_3^-$				1400	
19	$H_3C–(O–CH_2–CH_2)_nOSO_3^-$				1100	
20	$CH_3SO_3^-$	>20000			3200	
21	$CF_3SO_3^-$	>10000			1000	
22	Tos	17000			1900	
23	F^-	1200				
24	*Cl^-*	*>5000*	*>5000*	*7200*	*3600*	*720*
25	Br^-	>5000			2700	
26	I^-	>5000			3000	
27	$Co(CO)_4^-$				280	

exhibited a significant cytotoxicity. Especially the BBDB anion was found to have a considerable cytotoxic effect with an EC_{50} of 13 μM for its lithium salt. The commonly used anion bis(trifluoromethyl-sulfonyl)imide $N(SO_2CF_3)_2^-$ shows a moderate cytotoxicity (EC_{50} = 2200 μM).

Anion effects in imidazolium ionic liquids

All tested 1-alkyl-3-methyl-imidazolium ionic liquids in the present study with a chain length of C_2, C_4 and C_6 at the 1-position consistently show higher cytotoxicity—*i.e.* lower EC_{50} values—than the corresponding alkali salts of the same anions. The only exception can be found for the BOB anion where the EC_{50} value for the lithium salt is about equal to the value of the corresponding C_2MIM.

This suggests an intrinsic cytotoxic effect of the imidazolium cation moiety. Additionally the well known side chain length effect of the imidazolium cation headgroup was supported by our results when looking at ionic liquids of which all three different side chains were tested with the same anion (no. 1, 8, 24).

The influence of the anion moiety in ionic liquids on their cytotoxicity is identified by comparing the results obtained from one headgroup with one specific side chain length (columns 5, 6, 7 in Table 2) but different anions.

The biocompatible chloride anion has been selected for every imidazolium cation as inactive reference (emphasized by italic letters in line 24, Table 2) to indicate divergent cytotoxicity caused by the anion.

In order to identify significant anion effects for every single ionic liquid cation, we propose the concept of the anion effect ratio (see Digression 1) for ranking the relative influence of the anions in all tested ionic liquids on cytotoxicity. In Fig. 2 the side chain effect observed for the 1-alkyl-3-methyl-imidazolium ionic liquids (as chlorides) and the anion effects are illustrated in parallel to provide an overview of all ionic liquids, in which the anions exhibit a significant effect according to the anion effect ratio (AR).

Owing to the broad diversity in available anions for the C_4MIM cation the results obtained for the 20 ionic liquids from column 6 are presented first. Comparing all tested C_4MIM ionic liquids a diverse pattern of EC_{50} values can be observed. Three quarters of the tested anions did not or only marginally influence the cytotoxicity of the C_4MIM cation ($AR \leqslant 5$) but for five anions a significant ($AR > 5$) cytotoxic effect could be detected. It has to be noted that the magnitude of AR decreases with increasing cytotoxicity of the cation (Table 3, example no. 9), which is in line with the concentration addition principle detailed below.

Furthermore, for the C_2MIM and C_6MIM cations respectively five additional anions could be identified showing a significant effect on cytotoxicity (Fig. 2).

Digression 1: Anion effect ratio (AR)

To evaluate and discuss the influence of the anion moiety on the cytotoxicity of ionic liquids an anion effect ratio is defined.

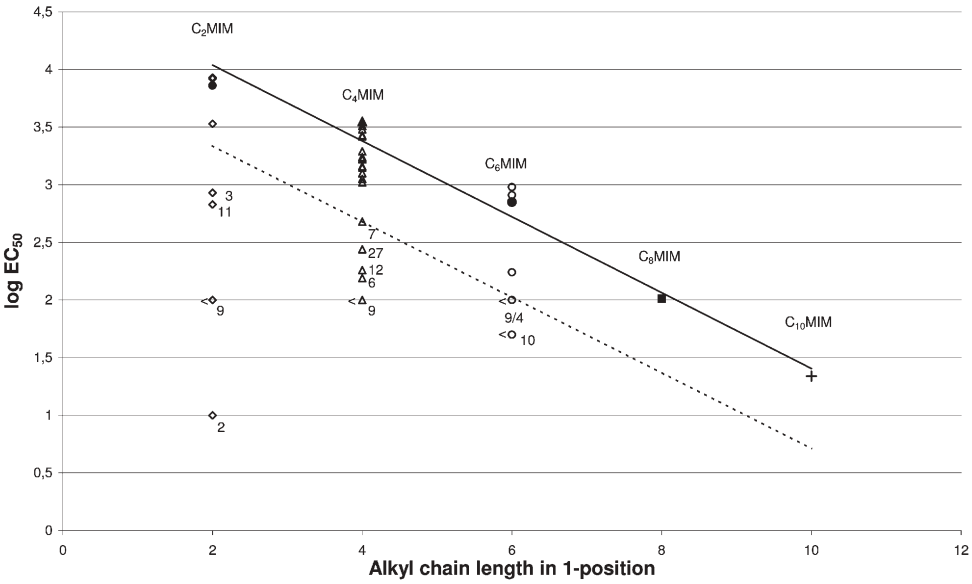


Fig. 2 Side chain and anion effect. The correlation between increasing chain length (C_2MIM (◇), C_4MIM (Δ), C_6MIM (○), C_8MIM (□), C_{10}MIM (+)) of the cation with chloride as reference counterion (closed symbols) versus the logarithm of the EC_{50} value is demonstrated. The bold line represents the linear regression curve for the chloride containing 1-alkyl-3-methylimidazolium cations, whereas the dashed line represents the benchmark (AR = 5) for significant anion effects (for details see Digression 1). Open symbols correspond to different anion species combined with the same cation. The numbered symbols (see Table 1) refer to anions which are classified as significantly cytotoxic because AR > 5. For ionic liquids containing the anions no. 4, 9 and 10 the EC_{50} values can only be estimated due to the low solubility of these compounds. Therefore the corresponding EC_{50} values are listed with "<" because the real test concentration of the substances is assumed to be lower than the nominal one.

The cytotoxicity of the ionic liquid is normalised on the cytotoxicity of the ionic liquids with chloride as counterion. Since the chloride anion does not exhibit intrinsic cytotoxic effects, these reference ionic liquids were taken to build up a linear regression line (see Fig. 2). This base line represents the intrinsic cytotoxicity of the cation moiety and is therefore used as benchmark for anion effects in the cytotoxicity assay.

Hence, the anion effect ratio can be expressed as the ratio of the EC_{50} value of the chloride containing reference ionic liquid $EC_{50}(R_x\text{MIMCl})$ and the EC_{50} value measured for the same cation combined with a different anion $EC_{50}(R_x\text{MIMY})$.

$$\text{AR} = \frac{EC_{50}(R_x\text{MIMCl})}{EC_{50}(R_x\text{MIMY})} \quad (1)$$

Applying this ratio to our results, it proved to be an adequate tool to roughly group the tested anions into two categories with respect to their potential of cytotoxic action. Using eqn (1) we classify anions in ionic liquids with AR values <5 to be non-cytotoxic or only marginally altering the cytotoxicity of the ionic liquid. In contrast, anions exhibiting AR values >5 are viewed as significantly influencing the cytotoxicity of the corresponding ionic liquid. This *a priori* specification results from the fact that with an AR > 5 the anion effect is statistically significant with respect to the confidence intervals (see ESI)† in our cytotoxicity tests.

To get a rapid overview of the anion effect ratios of all tested anions the line where AR = 5 is shown as a dashed line in Fig. 2.

Arranging the dose–response curves of selected ionic liquids in one graph (Fig. 3) illustrates these anion effects more clearly. Fig. 3 demonstrates that for example exchanging the ethylsulfate anion for the BBDB anion at the C_2MIM cationic moiety can modify the cytotoxicity by three orders of magnitude with cytotoxicities ranging from those for common molecular solvents like propanol down to highly cytotoxic isothiazolone biocides like *N*-octylisothiazolin-3-one (DCOIT).

Discussion

The results obtained in our study are discussed along to the following questions:

(i) Can the impact of the anions be attributed to physical and/or chemical properties of the anions and if so, which mode of action might be responsible for the observed cytotoxic effects?

(ii) Can the impact of the anions in ionic liquids be explained by the intrinsic cytotoxicity of the anion?

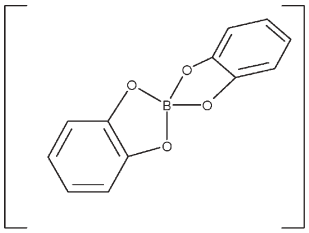
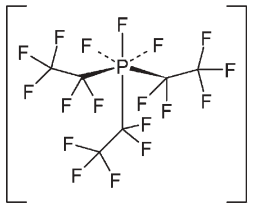
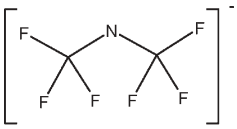
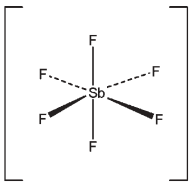
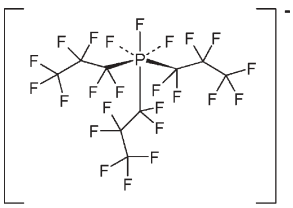
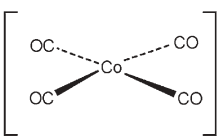
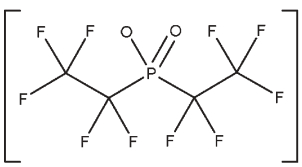
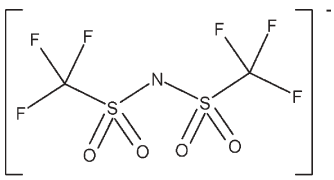
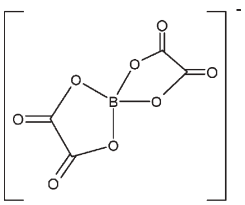
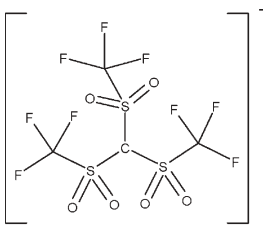
(iii) Is a simple model of mixture toxicity helpful in predicting the cytotoxicity of ionic liquids that have not been investigated yet?

The presented results clearly demonstrate that anions can influence the cytotoxicity of ionic liquids. In the following section the anions exhibiting a significant effect are analysed in detail using the T-SAR concept to elucidate physical and/or chemical properties that are responsible for the observed anion cytotoxicity.

T-SAR based discussion of the anion effect

Applying the T-SAR algorithm[9] to the anions showing a significant cytotoxic effect (Table 3) it becomes obvious that lipophilic interaction potentials of the anion side chains and

Table 3 Anion structures—shown in one isomeric form—exhibiting an AR > 5

Anion structure	Anion structure
	
No 2: **AR= 720 (C_2MIM)**	*No* 9: **AR>72 (C_2MIM) AR>36 (C_4MIM) AR>7 (C_6MIM)**
	
No 6: **AR=24 (C_4MIM)**	*No* 12: **AR=20 (C_4MIM)**
	
No 10: **AR>14 (C_6MIM)**	*No* 27: **AR=13 (C_4MIM)**
	
No 11: **AR=11 (C_2MIM)**	*No* 7: **AR=8 (C_4MIM)**
	
No 3: **AR=8 (C_2MIM)**	*No.* 4: **AR>7 (C_6MIM)**

the chemical stability of the anion moiety itself are the crucial features with respect to the observed cytotoxicity.

Concerning the chemical stability under test conditions (37 °C, 44 h incubation, pH 7) hydrolysis reactions form the main type of chemical transformations certain anions may undergo. For some anions hydrolysis has been investigated and recently been confirmed.[26–28] Preliminary results from our own investigations support that compound no. 2, 3, 6, and 12 are also vulnerable to hydrolytic cleavage and degradation. Some of the chemical species formed by hydrolysis may exhibit a high intrinsic reactivity causing cytotoxic effects.

Especially the hydrolysis of fluorine containing anions is of toxicological interest owing to the possibility of a formation of free fluoride ions. As sodium salts, the fluoride anion shows a cytotoxic effect (EC_{50} ~ 1200 μM) in our investigations. Additionally it is known that the fluoride ion is a potent inhibitor of the Na^+-K^+-ATPase which is located at the cell surface and thus may interfere with processes essential in cell self-maintenance.[29]

Beside the possible intrinsic chemical reactivity it is remarkable that the major part of anions shown in Table 3 contain moieties with lipophilic interaction potential. This facilitates the interaction of the respective anions with cell membranes and hydrophobic protein domains, potentially disrupting essential physiological functions. Such a mode of action based on compound lipophilicity is well known for a broad variety of unreactive chemical substances.[20,30–32]

Taking a closer look at the structures in Table 3, it is obvious that highly fluorinated alkyl side chains are predominantly but not exclusively accountable for the lipophilicity. The influence of the degree of fluorination on cytotoxicity is supported by the case of C_4MIM CH_3SO_3 displaying significantly lower (validated by *t*-test analysis with $n = 9$ and $\alpha = 0.05$) cytotoxicity (EC_{50} = 3200 μM) in comparison to C_4MIM CF_3SO_3 (EC_{50} = 1000 μM). Since trifluoromethanesulfonate is a stable anion under physiological conditions, the increase in cytotoxicity in this case cannot be due to the formation of HF, but results from the increased lipophilicity of the anion.

To sum up, it can be assumed that the intrinsic reactivity of hydrolysis products and especially effects owing to lipophilicity are possible causes of cytotoxicity.

Discussion of mixture toxicity

As discussed in the previous section the anion species exhibit an impact on the cytotoxicity of ionic liquids. Thus, the question arises whether the observed cytotoxicity of ionic liquids is based on the sum of the intrinsic cytotoxicities of the cation and the anion moieties?

To answer this question the simple model of concentration addition is applied (for details see Digression 2 and the literature cited therein).[33–39] The comparison between calculated and measured cytotoxicity values (Table 4) indicates a good correlation within a factor of two. Therefore we conclude that for the compounds shown in Table 4 the intrinsic cytotoxicities of the cation and the anion are responsible for the total cytotoxicity of a certain ionic liquid.

However, for the $(CF_3SO_2)_2N$ anion in combination with different imidazolium cations (shown in Table 5) we experimentally found a significantly higher cytotoxicity as calculated from the model of concentration addition. For all three tested imidazolium ionic liquids the experimentally derived EC_{50} values are around three times lower than the calculated ones. This overadditive effect may be due to the temporary formation of direct ion pairs in aqueous solutions composed of the cation and the anion moiety. Ion pair formation can result in a significantly higher bioavailability of the particular ionic liquid amplifying membrane interactions and entailing stronger cytotoxic effects.

Substance	EC_{50} [μM]
N-octylisothiazolin-3-one (DCOIT) **(1)**	1
N-octylisothiazolin-3-one (OIT)	2
N-methylisothiazolin-3-one (MIT)	10
C_2MIM BBDB **(2)**	10
C_4MIM $N(CF_3)_2$ **(3)**	150
C_4MIM] CF_3SO_3 **(4)**	1000
C_2MIM $C_2H_5OSO_3$ **(5)**	8500
Propanol **(6)**	60.000
Ethanol	700.000
Methanol	1.600.000
Acetonitril	3.000.000

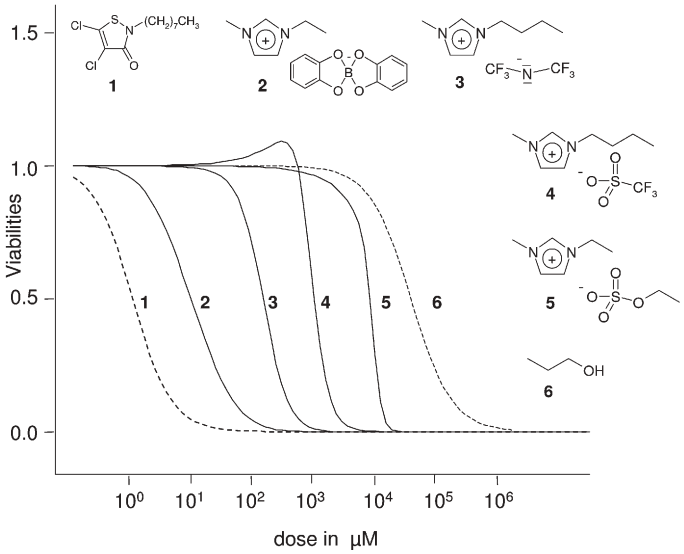


Fig. 3 Ranges of cytotoxicity and dose–response curves. The table on the left shows EC_{50} values of 1-alkyl-3-methylimidazolium salts with different chain lengths. The dashed lines represent reference dose–response curves for a common organic solvent (**6**) and a highly reactive biocide (**1**), respectively. The dose–response curve of C_4MIM CF_3SO_3 (no. 4) shows a hormetic effect to which no significance is attributed in the context of the present study.

Applying the model of concentration addition to our results indicate that the cytotoxicity for most of the tested cation and anion combinations can be reduced to the intrinsic cytotoxicities of the cation and anion species, respectively. Thus, the model of concentration addition seems to be a useful tool in the prospective prediction of the minimum cytotoxicities of combinations of ionic liquid cations and anions not realised so far.

Nevertheless, the example of the $(CF_3SO_2)_2N$ anion shows that overadditive combination effects have to be considered in the risk assessment of ionic liquids and require further testing of newly developed cations and anions.

Digression 2: Mixture toxicity

The model of concentration addition[30–32] is frequently used to describe mixture effects in toxicological and ecotoxicological studies.[33,34] The basic precondition for applying this model is the assumption that the single substances of a mixture under investigation are acting by the same or at least closely related modes of toxic action and at the same target site in the test systems.[32,35] Given this precondition the effect concentration EC_X(Mix) of a mixture of n different test substances producing a defined effect level X can generally be expressed as follows:

$$EC_X(\text{Mix}) = \left(\sum_{i=1}^{n} \frac{P_i}{EC_X(S_i)} \right)^{-1} \quad \text{with} \tag{2}$$

$$P_i = \frac{C_{S_i}}{C_{(\text{Mix})}} \tag{3}$$

Where the $EC_X(S_i)$ value is the effect concentration of a single substance out of the test mixture at which the effect X can be detected in the same test system. P_i represents the fraction of substance S_i in the test mixture.

Since most ionic liquids represent a binary mixture with equal concentrations of the cation and the anion species and due to the fact that we measured EC_{50} values (*i.e.* effect level X is 50%) eqn (2) can be rearranged to:

$$EC_{50}^{1+2} = \frac{EC_{50}^{1}\, EC_{50}^{2}}{EC_{50}^{1} + EC_{50}^{2}} \tag{4}$$

Table 4 Comparison between measured (bold letters) and calculated EC_{50} values (in parentheses) according to the model of concentration addition. Presented are all imidazolium salts for which the EC_{50} values of the anion moiety as sodium or lithium salts were tested and detectable

	EC_{50} values/μM	
	C_2MIM	C_4MIM
BBDB	**10** (13)	
BOB	**860** (890)	
$(CN)_2N^-$		**1400** (2900)
SbF_6^-		**180** (190)
HSO_4^-		**1900** (2500)
$C_8H_{17}OSO_3^-$		**1700** (1600)
Tos		**1900** (3000)

Table 5 Overadditive effects in ionic liquids. Presented are the measured and calculated (see Digression 2) EC_{50} values for three imidazolium cations with increasing chain length. The C_8MIM cation was added to the test kit because for the C_2MIM cation the corresponding $N(CF_3SO_2)_2$ salt was not available. The calculated factor describes the ratio of the measured and the calculated cytotoxicity for the imidazolium cation species combined with the $N(CF_3SO_2)_2$ anion. Factors exceeding a value of one indicate overadditive effects

	EC_{50} values/μM			
	Li^+	C_4MIM	C_6MIM	C_8MIM
Cl^-		3600	720	100
$N(CF_3SO_2)_2^-$	2200	480	180	38
Calculated $N(CF_3SO_2)_2^-$		1400	540	96
Factor		2.9	3.0	2.5

Now the EC^{1+2}_{50} describes the expected EC_{50} value of a certain ionic liquid. Furthermore the EC^{1}_{50} and EC^{2}_{50} values are representing the EC_{50} of the cation combined with chloride as reference and of the anion tested as lithium or sodium salt, respectively.

Given the EC^{1}_{50} values of a set of cations and the EC^{2}_{50} values of a set of different anions one can estimate the EC_{50} values of every possible ionic liquid according to eqn (4) and compare the obtained results with the measured EC_{50} values in our test system.

Assuming that mode of toxic action and target site are similar or at least closely related for the cation and the anion moieties forming an ionic liquid one can conclude that mixture effects are due to pure concentration addition if calculated and measured EC_{50} values are roughly identical. However, if under the same preconditions the calculated and the measured EC_{50} values are significantly different there are two possibilities. On the one hand an underadditive effect of a mixture is stated if a calculated EC_{50} value is lower (higher cytotoxicity) compared to the experimentally derived EC_{50} value. On the other hand overadditive effects of a test mixture can be identified if the measured EC_{50} value is lower than the effect concentration derived from eqn (4).

Even in the case where mode of action and target sites of cations and anions are not necessarily the same the model presented above is useful in the prospective risk evaluation[36] of ionic liquids not yet synthesised.

Conclusion

Using the IPC-81 rat leukemia cell line as test system we could demonstrate that most of the commercially available anions investigated showed no or only marginal cytotoxic effects. However, for certain anions a significant influence on the ionic liquid cytotoxicity is demonstrated for the first time.

Therefore the term 'anion effect' is proposed for some anions comparable to the side chain effect established for specific cations. In particular, anionic moieties with lipophilic and hydrolysable structural elements seem to be of considerable relevance with respect to the observed cytotoxic effects.

Concerning mixture toxicity, analysis of our cytotoxicity data proved the model of concentration addition to be a useful tool for the prospective estimation of ionic liquid cytotoxicity. Additionally, the comparison of experimental and modelled data suggests overadditive effects of certain anion and cation combinations that might result from ion pair formation.

In general, the model-based prospective estimation of the cytotoxicity combined with experimentally derived cytotoxicity data for anions and cations complemented by consideration of structure–property relationships opens up the opportunity to overcome the above mentioned dilemma of an unmanageable pool of possible ionic liquids.

In this iterative approach chemists creativity is guided by the structural properties of cation and anion species, which leads to a reduced number of task specific and intrinsically safer ionic liquids. Through such a process more sustainable ionic liquids can be realised.

Nevertheless, to reach a valid data pool for the environmental risk assessment of ionic liquids, in particular including the anion species, the limited cytotoxicity data need to be expanded by data from more complex biological test systems. Further studies to verify the observed anion effect are in progress.

Experimental

Chemicals

The 1-alkyl-3-methylimidazolium cations are abbreviated according to their alkyl chain length with C_2MIM, C_4MIM, C_6MIM, C_8MIM, and C_{10}MIM. The structures and the abbreviations of the anions are listed in Table 1.

The test substances were received by the companies listed below.

Merck KGaA (Darmstadt, Germany): C_2MIM BF_4, C_2MIM BBDB, C_2MIM BOB, C_2MIM PF_6, C_2MIM $(C_2F_5)_2P(O)O$, C_2MIM Cl, C_2MIM $(C_2F_5)_3PF_3$, C_4MIM BF_4, C_4MIM $N(CN_2)$, C_4MIM $N(CF_3)_2$, C_4MIM Tos, C_4MIM $N(SO_2CF_3)_2$, C_4MIM PF_6, C_4MIM SbF_6, C_4MIM CF_3SO_3, C_4MIM Cl, C_4MIM Br, C_4MIM I, C_4MIM $Co(CO)_4$, C_4MIM $(C_2F_5)_3PF_3$, C_6MIM BF_4, C_6MIM $(CF_3SO_2)_3C$, C_6MIM $N(CF_3SO_2)_2$, C_6MIM PF_6, C_6MIM $(C_2F_5)_3PF_3$, C_6MIM $(C_3F_7)_3PF_3$, C_6MIM Cl, C_8MIM Cl, C_8MIM $N(SO_2CF_3)_2$, C_{10}MIM Cl, Li BBDB, Li BOB, LiCl, Na Tos, NaF.

Solvent Innovation (Köln, Germany): C_2MIM $C_2H_5OSO_3$, C_4MIM BF_4, C_4MIM CH_3OSO_3, C_4MIM $C_8H_{17}OSO_3$, C_4MIM $H_3CO(CH_2)_2O$–$(CH_2)_2OSO_3$, C_4MIM H_3C–$(O$–CH_2–$CH_2)_nOSO_3$, C_6MIM BF_4, Na $C_8H_{17}OSO_3$.

Acros Organics (Geel, Belgium): $NaN(CN)_2$, NaSCN, $NaHSO_4$, $NaCH_3OSO_3$, NaCl, NaBr, NaI.

Fluka (Buchs, Switzerland): C_4MIM PF_6, C_4MIM SCN, C_4MIM HSO_4, C_4MIM CH_3SO_3, Li $N(CF_3SO_2)_2$, Na CH_3SO_3, Na CF_3SO_3.

Lancaster (Frankfurt, Germany): $NaBF_4$, $NaSbF_6$.

Purity

The identity of the cation and anion species was confirmed *via* ESI-MS analysis (except for the sodium, lithium, fluoride, chloride ions). Out of the 53 investigated substances, 23 ionic liquids (C_2MIM $C_2H_5OSO_3$, C_2MIM BOB, C_2MIM BBDB, C_4MIM BF_4, C_2MIM Cl, C_4MIM Tos, C_4MIM Br, C_4MIM $C_8H_{17}OSO_3$, C_4MIM CH_3OSO_3, C_4MIM $H_3CO(CH_2)_2O$–$(CH_2)_2OSO_3$, C_4MIM H_3C–$(O$–CH_2–$CH_2)_nOSO_3$, C_4MIM CF_3SO_3, C_4MIM SbF_6, C_4MIM $N(CF_3)_2$, C_4MIM $N(SO_2CF_3)_2$, C_4MIM $N(CN_2)$, C_6MIM $(C_2F_5)_3PF_3$, C_6MIM BF_4, C_6MIM Cl, C_6MIM PF_6, C_6MIM $N(CF_3SO_2)_2$, C_8MIM Cl, C_{10}MIM Cl) and 3 alkali salts ($NaBF_4$, $NaC_8H_{17}OSO_3$, $NaCF_3SO_3$) were tested for volatile impurities by gas chromatography. Measurements were performed at 80 °C (determination of low-boiling contaminations) and 205 °C (determination of high-boiling contaminations). All tested compounds contain less than 1% of low-boiling impurities and in general less than 5% high-boiling impurities. For some compounds (C_4MIM $N(CF_3)_2$, C_6MIM Cl, C_8MIM Cl, C_4MIM $C_8H_{17}OSO_3$, Na $C_8H_{17}OSO_3$, C_{10}MIM Cl) a higher amount of impurities ($\leqslant$10%) at 205 °C was detectable. In these cases, pyrolysis of the substances to volatile degradation

products is the likely cause. Detailed information about the analytical methods and results will soon be published elsewhere.

Cell culture

Cytotoxicity of ionic liquids was determined for the promyelocytic leukemia rat cell line IPC-81.[21] Cultures of IPC-81 were grown in RPMI medium (with L-glutamine, without $NaHCO_3$, supplemented with 1% penicillin–streptomycin and 1% glutamine, pH 7) with 10% horse serum at 37 °C (5% CO_2).

Cell viability assay

Cell viability was measured using a colorimetric assay for 96 well plates with 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium monosodium salt (WST-1) reagent.[23] Each plate contained blanks, controls, and two substance dilution series with three replicates each. Stocks of ionic liquids were prepared in culture medium with 0.5% dimethylsulfoxide (DMSO) to improve the solubility of the substances. This DMSO concentration has been proven not to be cytotoxic. All compounds were tested in a concentration range from about 1 μM up to at least 1 mM. Detecting no toxic effects within that range the concentration of the test substance was extended up to 20 mM depending on their solubility. The dilution series of the tested substances in medium were made in 96 well plates. Cells were added to the plates in a concentration of 15×10^5 cells mL^{-1} (in RPMI with 8% fetal calf serum) and cultivated for 48 h. After 44 h, 10 mL of WST-1 (diluted 1 : 4 with phosphate buffer) were added and cells were incubated for an additional 4 h. Cell viability was measured at 450 nm in a microplate reader (MRX Dynatech). Cytotoxicity of the compounds was expressed as percentage cell viability measured as WST-1 reduction compared to controls. The cell viability assays were generally carried out for a 1 : 1 dilution series. Each dose response curve was recorded for at least 9 parallel dilution series on three different 96 well plates. Positive controls with Carbendazim were checked in regular intervals.

Effect data modeling

If feasible, dose–response curves (see examples in Fig. 3) were fitted to the dose–response data with the nonlinear least-squares method using the logit model for the relation of cell viability to the decadic logarithm of the tested concentrations, which can be written as

$$p = \frac{1}{1 + (c/c')^b} \quad (5)$$

where c is the concentration of the substance to which the cells are exposed, p is the physiological response, normalised with positive and negative controls to the interval from 1 ($c = 0$) to 0 (positive control). c' represents the EC_{50}, and b is the slope of the function on a logit-log-scale.[40]

In many cases the cell viability initially increased with increasing concentration of the test substance, before it was finally reduced with a further increase of the concentration. Dose response curves showing such a subtoxic stimulus were fitted using the linear-logistic (linlogit) model[41] as parameterised by Van Ewijk and Hoekstra.[40]

$$p = \frac{1 + fc}{1 + (2fc' + 1)(c/c')^{b'}} \quad (6)$$

According to eqn (6) b' is a parameter without intuitive interpretation and f is the parameter describing hormesis. If $f > 0$ the curve shows maximum at subtoxic concentrations. In one case, neither the logit nor the linlogit model could be fitted to the data, so a probit fit (cumulative lognormal distribution) was used. Calculations were performed with the software library drfit for the R language and environment for statistical computing.[42,43]

The confidence intervals of the fitted EC_{50} values are reported in the ESI.†

Acknowledgements

The authors gratefully thank Thomas Colnot, Christian Jungnickel, Kerstin Mölter, and Reinhold Störmann for helpful discussions. Furthermore special thanks are given to both Merck KGaA and the Solvent Innovation companies for providing chemicals and to Merck KGaA for their generous support within our strategic partnership.

References

1 P. Wasserscheid and T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH-Verlag, Weinheim, 2002.
2 T. Welton, *Chem. Rev.*, 1999, **99**, 8, 2071–2083.
3 R. A. Sheldon, R. M. Lau, M. J. Sorgedrager, F. van Rantwijk and K. R. Seddon, *Green Chem.*, 2002, **4**, 2, 147–151.
4 F. Endres, *ChemPhysChem*, 2002, **3**, 2, 144–154.
5 J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 223–236.
6 M. Freemantle, *Chem. Eng. News*, 2000, **78**, 20, 37–50.
7 B. Jastorff, K. Mölter, P. Behrend, U. Bottin-Weber, J. Filser, A. Heimers, B. Ondruschka, J. Ranke, M. Schaefer, H. Schröder, A. Stark, P. Stepnowski, F. Stock, R. Störmann, S. Stolte, U. Welz-Biermann, S. Ziegert and J. Thöming, *Green Chem.*, 2005, **7**, 362–372.
8 C. A. Doose, J. Ranke, F. Stock, U. Bottin-Weber and B. Jastorff, *Green Chem.*, 2004, **6**, 5, 259–266.
9 B. Jastorff, R. Störmann and U. Wölke, *Struktur-Wirkungs-Denken in der Chemie*, Universitätsverlag Aschenbeck & Isensee, Bremen, Oldenburg, 2004.
10 B. Jastorff, R. Störmann, J. Ranke, K. Molter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nuchter, B. Ondruschka and J. Filser, *Green Chem.*, 2003, **5**, 2, 136–142.
11 F. Stock, J. Hoffmann, J. Ranke, R. Störmann, B. Ondruschka and B. Jastorff, *Green Chem.*, 2004, **6**, 6, 286–290.
12 J. Pernak, K. Sobaszkiewicz and I. Mirska, *Green Chem.*, 2003, **5**, 1, 52–56.
13 R. P. Swatloski, J. D. Holbrey, S. B. Memon, G. A. Caldwell, K. A. Caldwell and R. D. Rogers, *Chem. Commun.*, 2004, 6, 668–669.
14 J. Ranke, K. Molter, F. Stock, U. Bottin-Weber, J. Poczobutt, J. Hoffmann, B. Ondruschka, J. Filser and B. Jastorff, *Ecotoxicol. Environ. Saf.*, 2004, **58**, 3, 396–404.
15 P. Stepnowski, A. C. Skladanowski, A. Ludwiczak and E. Laczynska, *Hum. Exp. Toxicol.*, 2004, **23**, 11, 513–517.
16 M. T. Garcia, N. Gathergood and P. J. Scammells, *Green Chem.*, 2005, **7**, 1, 9–14.
17 K. M. Docherty and C. F. Kulpa, *Green Chem.*, 2005, **7**, 4, 185–189.
18 R. J. Bernot, E. E. Kennedy and G. A. Lamberti, *Environ. Toxicol. Chem.*, 2005, **24**, 7, 1759–1765.

19 A. Latala, P. Stepnowski, M. Nedzi and W. Mrozik, *Aquat. Toxicol.*, 2005, **73**, 1, 91–98.
20 J. Ranke, F. Stock, A. Müller, S. Stolte, R. Störman, U. Bottin-Weber and B. Jastorff, 2006, submitted.
21 N. Lacaze, G. Gombaud-Saintonge and M. Lanotte, *Leuk. Res.*, 1983, **7**, 2, 145–154.
22 M. Ishiyama, M. Shig, M. Mizoguchi and P. G. He, *Chem. Pharm. Bull.*, 1993, **44**, 6, 1118–1122.
23 M. V. Berridge, A. S. Tan, K. D. McCoy and R. Wang, *Biochemica*, 1996, **4**, 14–19.
24 A. Siol, *PhD Thesis*, University of Bremen, 2002.
25 F. Stock, *PhD Thesis*, University of Bremen, 2004.
26 G. A. Baker and S. N. Baker, *Aust. J. Chem.*, 2005, **58**, 3, 174–177.
27 R. P. Swatloski, J. D. Holbrey and R. D. Rogers, *Green Chem.*, 2003, **5**, 4, 361–363.
28 C. Villagran, M. Deetlefs, W. R. Pitner and C. Hardacre, *Anal. Chem.*, 2004, **76**, 7, 2118–2123.
29 F. A. Smith, in *Handbook of hazardous materials*, ed. M. W. Corn, Academic Press, San Diego, 1993, pp. 277–283.
30 B. Antkowiak, *Naturwissenschaften*, 2001, **88**, 5, 201–213.
31 B. I. Escher and J. L. M. Hermens, *Environ. Sci. Technol.*, 2002, **36**, 20, 4201–4217.
32 H. H. Meyer, *Arch. Exp. Pathol. Pharmakol.*, 1899, **42**, 109–118.
33 S. Loewe, *Klin. Wochenschr.*, 1927, **6**, 1077–1085.
34 S. Loewe, *Arzneim. Forsch.*, 1953, **3**, 285–290.
35 R. L. Plackett and P. S. Hewlett, *J. R. Stat. Soc.*, 1952, **14**, 2, 141–163.
36 R. Altenburger, W. Boedeker and M. Faust, in *Handbook of hazardous materials*, ed. M. W. Corn, Academic Press, San Diego, 1993; pp. 15–27.
37 L. H. Grimme, R. Altenburger, T. Backhaus, W. Boedeker, M. Faust and M. Scholze, UFZ-Bericht 25, UFZ-Umweltforschungszentrum, Leipzig-Halle GmbH, 1998.
38 W. R. Greco, G. Bravo and J. C. Parsons, *Pharmacol. Rev.*, 1995, **47**, 2, 331–385.
39 M. C. Berenbaum, *J. Theor. Biol.*, 1985, **114**, 3, 413–431.
40 P. H. Van Ewijk and J. A. Hoekstra, *Ecotoxicol. Environ. Saf.*, 1993, **25**, 1, 25–32.
41 P. Brain and R. Cousens, *Weed Res.*, 1989, **29**, 93–96.
42 R Development Core Team, *R: A language and environment for statistical computing*, R Foundation for Statistical Computing, Vienna, Austria, 2005, computer program.
43 J. Ranke, *Drfit: Dose–response data evaluation*, 2005, computer program.

Chitin and chitosan dissolved in ionic liquids as reversible sorbents of CO_2†

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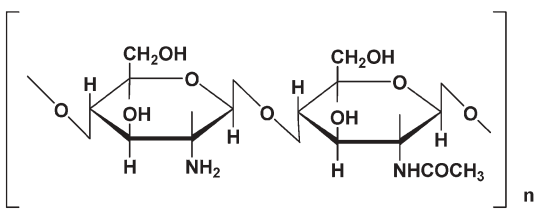
Received 6th December 2005, Accepted 2nd February 2006
First published as an Advance Article on the web 27th February 2006
DOI: 10.1039/b517297g

A novel dissolving process for chitin and chitosan has been developed by using the ionic liquid 1-butyl-3-methyl-imidazolium chloride ([Bmim]Cl) as a solvent, and a novel application of chitin and chitosan as substitutes for amino-functionalized synthetic polymers for capturing and releasing CO_2 has also been exploited based on this processing strategy.

Introduction

Ionic liquids (ILs), combining good and tuneable solubility properties with a negligible vapor pressure and excellent thermal stabilities, have recently received much attention as green solvents as a result of the development of green chemistry and the requirement for environmental protection. Ionic liquids have been applied as alternative solvents in many catalytic organic transformations.[1] They have also been used recently for dissolving biological macromolecules that are linked together by intermolecular hydrogen bonds such as carbohydrates, cellulose, wool keratin and silk fibroin,[2] and these biomaterials could be regenerated, derivated and functionalized through these processing platforms. For example, Wu *et al.* reported the homogeneous acetylation of cellulose in an ionic liquid, 1-allyl-3-methylimidazolium chloride. Turner *et al.*[3] reported a novel method for introducing enzymes into cellulosic membranes by using a cellulose/ionic liquid dissolution and regeneration process. Chitosan, a natural biomaterial, is an *N*-deacetylated product of chitin, which is the second most abundant natural polymer after cellulose and has a similar structure to cellulose.[4] Chitin has two hydroxyl groups while chitosan has one amino group and two hydroxyl groups in the repeating hexosaminide residue (Scheme 1). In recent years, alongside the rapid development in materials and biomedical sciences, and the rise of environmental protection consciousness, there has been much scientific and industrial interest in utilizing chitin and chitosan for a diverse range of applications such as pharmaceutical, waste water treatment, cosmetics, drug delivery, heavy metal chelation, heterogeneous catalysts and many other attractive utilizations.[5] For these applications, especially when chemical modification of these biopolymers is needed, it is essential to form a stable homogeneous chitin or chitosan solution in order to improve the efficiency of modification. However, strong inter- and intramolecular hydrogen bonding between the polymer chains decreases their solubility in many organic solvents. Traditionally, concentrated solutions of hydrochloric acid and sulfuric acid,[6] and an alkaline–ice mixture were used to dissolve chitin.[7] Nevertheless, these solvents are highly corrosive and the polymer solutions are not stable because chitin undergoes hydrolysis in strongly acidic conditions. In addition, hexafluoroisopropyl alcohol, hexafluoroacetone, DMAc–LiCl and solvents based on chloroalcohols in conjunction with aqueous solutions of mineral acids or organic acids, *etc.* can also dissolve chitin or chitosan.[8] Chitosan is an easily soluble polymer and is soluble in dilute aqueous solutions of organic and mineral acids, but an alkaline solution treatment process is necessary to remove the acid after the process.[9] Furthermore, the polyelectrolyte solutions formed had limited application as transition metal sorbents[10] and drug carriers,[11] because bioactive agents may be affected by acetic acid. Consequently, a new processing strategy for developing potential applications of these biorenewable resources is still challenging work.



Scheme 1 The structure of chitosan.

The purpose of the present work is to utilize the ionic liquid [Bmim]Cl, which has a strong ability to disrupt hydrogen bonds, to dissolve chitin and chitosan under suitable conditions, and to explore new applications of these bio-feedstocks based on this novel processing platform.

Results and discussion

The ionic liquid [Bmim]Cl used in this dissolving process was synthesized according to a literature method[12]and dried at 100 °C in a vacuum oven for 48 hours prior to the experiments. Chitosan (with a degree of deacetylation of 88% and an average molecular weight of 3×10^5 to 4×10^6) and chitin were purchased from Sinopharm Chemical Reagent Co. Ltd, and used directly without further purification. All dissolution experiments were performed in a 50 ml three-necked flask using 10 g of ionic liquid under an inert atmosphere of N_2,

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with a mechanical stirrer. The temperature of the dissolving process was controlled by an oil bath at 110 °C. The chitin or chitosan powder was added in portions of only 1 wt% of ionic liquid each time, and the solid allowed to dissolve before each new addition. It is easy to prepare 10 wt% chitin/IL and 10 wt% chitosan/IL solutions in 5 hours, and the resulting chitin/IL solution was clear and viscous. However, 10 wt% chitosan/IL solution was semi-clear and viscous. Chitin and chitosan were regenerated when methanol or water was added into the solution. The chitin and chitosan regenerated from methanol were verified by IR analysis, TGA analysis (see Supporting information†) and wide angle X-ray diffraction (WAXD, Fig. 1).

In order to further prove the degree of dissolution of chitin and chitosan in the ionic liquid, the crystal structure of 10 wt% chitin/IL and chitosan/IL solutions were determined by WAXD. From Fig. 1, we can see that the chitin/IL solution shows no diffraction pattern, which indicates that the crystalline domains of chitin have been disrupted completely by the ionic liquid during the dissolving process. However, the ionic liquid solution of chitosan shows a slight, broad diffraction peak centered near $2\theta = 25°$, which can not be eliminated by decreasing the chitosan concentration or prolonging the time of dissolution. This result implies that partial crystalline domains of chitosan are not disrupted completely by [Bmim]Cl during this dissolving process. Anyway, we can conceive that such a treatment should make the active hydroxyl groups and amino groups of chitosan and chitin more flexible and active than those of heterogeneous chitosan and chitin, and provide reactants with easy access to these sites.

After the chitin/IL and chitosan/IL solutions were obtained, we examined their potential applications based on this new processing platform. Development of efficient methods for CO_2 recovery from industrial waste gases *etc.* is very important in relation to both reutilization of CO_2 as a carbon resource and environmental issues concerned with the greenhouse effect. One of the most commonly used processes for CO_2 recovery is chemically reversible CO_2 fixation by amines at room temperature to give ammonium carbamates, the CO_2 being released from the ammonium carbamates upon heating.[13] Amino-functionalized synthetic polymers and ionic liquids have also been developed for the fixation of CO_2 based on this principle.[14] Chitosan has one amino group and two hydroxyl groups in the repeating hexosaminide residue. Hence chitosan can be considered as a natural polyamine, and it could be a much more suitable alternative amino-functionalized polymer to fix CO_2 under suitable conditions. But the drawbacks of the traditional dissolving process using aqueous acid restrict its applications in this aspect. The ability of [Bmim]Cl to destroy hydrogen bonds makes the amino group in chitosan free from the restraint of the intermolecular hydrogen bonds and exposed completely. This makes the amine group react with other chemical reagents easily, and hence this novel dissolving process can overcome the drawbacks of traditional dissolving processes and make the natural polyamine a substitute to synthetic amino-functionalized polymers for fixation and release of CO_2 (Scheme 2).

On the basis of the discussion mentioned above, we carried out CO_2 fixation and release using chitin/IL and chitosan/IL solutions. The experiments were performed at 30 °C and 1 atm CO_2 pressure. Fixing efficiency [(mmol of CO_2/mmol of ionic liquid) × 100%] was estimated from the weight increase in the reaction mixture. A detailed description of the apparatus and the experimental procedure are given in the Supporting information†. It can be seen from Fig. 2 that [Bmim]Cl and chitosan powder have almost no ability to absorb CO_2 (Fig. 2, curves c and d), but the 10% wt chitin/IL or chitosan/IL solutions both show good capacity to capture CO_2 (Fig. 2, curves a and b). For example, at equilibrium, the chitosan/IL and chitin/IL solutions exhibited approximately 8.1% and 3.8% CO_2 fixing efficiency, respectively. These results further prove the important effect of chitin and chitosan in this CO_2 absorption process. From Fig. 2 (curves a and b), we can also find that the sorption efficiency of chitosan/IL solution is much higher than that of chitin solution, which is probably due to the fact that there are many amino groups in chitosan and none in chitin, and demonstrates the key effect of free amino groups in the absorption of CO_2. Hence, it is reasonable to consider that physically dissolved carbon dioxide is responsible for the CO_2 sorption capacity of chitin/IL solution, and both physically dissolved CO_2 and chemically bound carbon dioxide are responsible for the effective CO_2 sorption

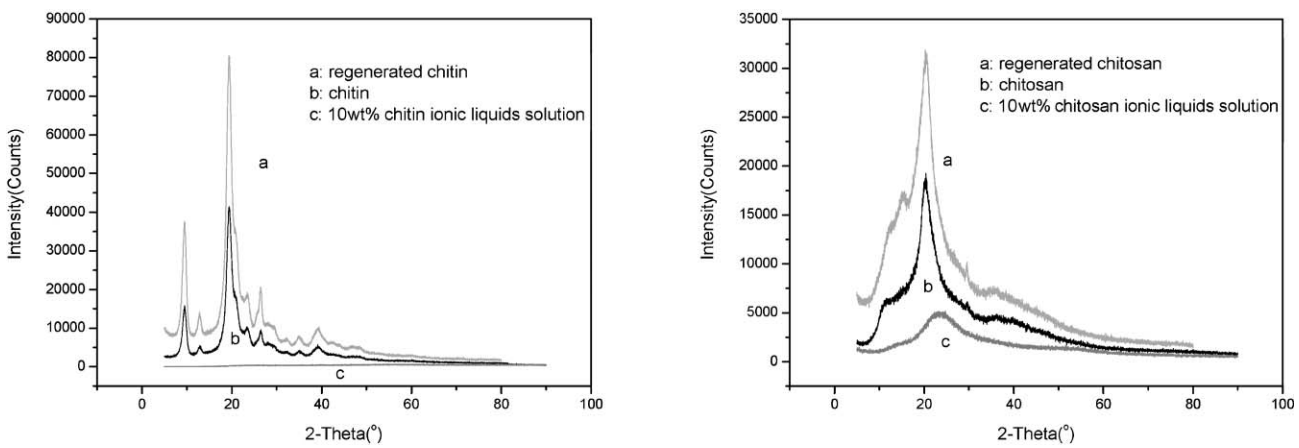
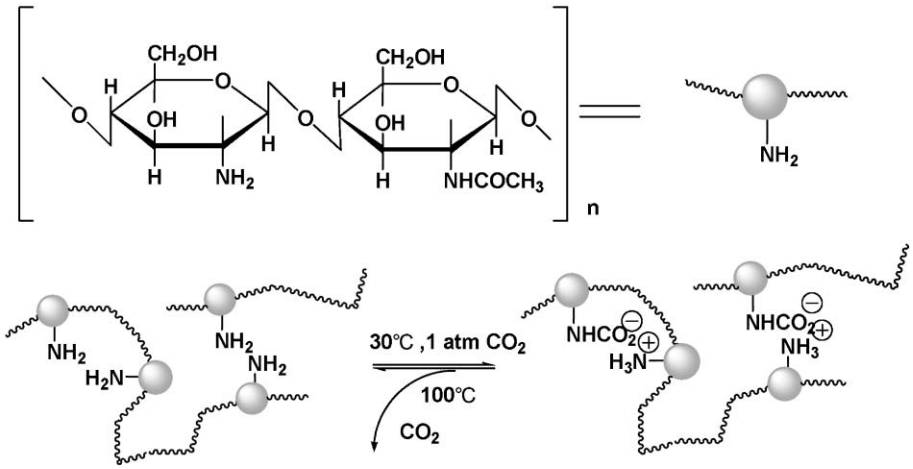


Fig. 1 a: WAXD comparison of chitin, regenerated chitin from methanol and 10 wt% chitin/IL solution; b: WAXD comparison of chitosan, regenerated chitosan from methanol and 10 wt% chitosan/IL solution.



Scheme 2 Reversible covalent chemistry between CO_2 and amines linked to the chitosan polymer chain.

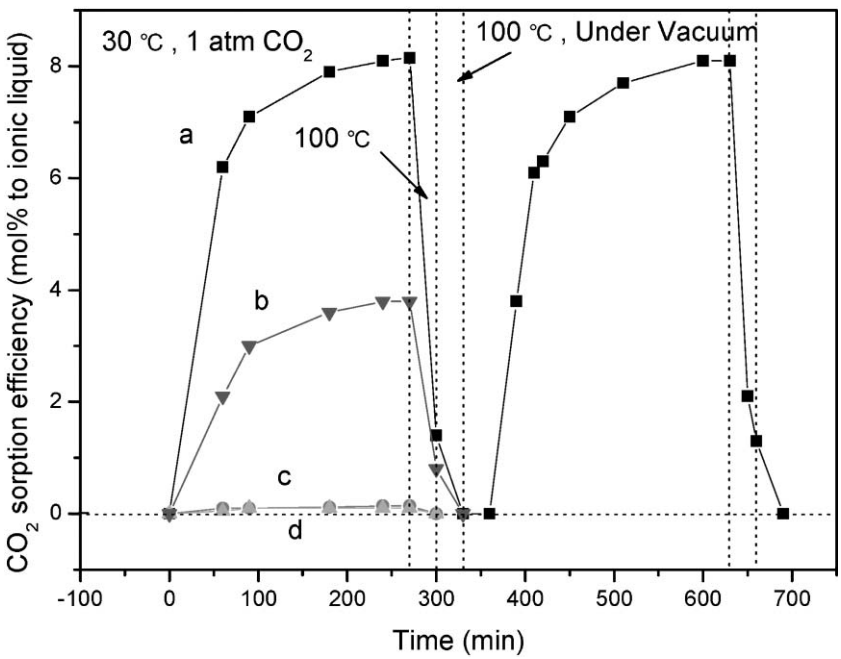


Fig. 2 Reversible CO_2 fixation and release by chitin/IL and chitosan/IL solution. a: 10 wt% chitosan/IL solution; b: 10 wt% chitin/IL solution; c: [Bmim]Cl; d: 1 g chitosan powder under 1 atm CO_2.

capacity of chitosan/IL solution. As 1 g of chitosan with 88% degree of deacetylation will have 5.3 mmol of amino groups, if we suppose that all the amino groups are converted to ammonium salts, the amount of chemically bound carbon dioxide should be 2.6 mmol, corresponding to a fixing efficiency of 4.5%. In the present study, the CO_2 fixing efficiency of 10% wt chitosan/IL solution is 8.1%, therefore the extra CO_2 sorption capacity of chitosan/IL solution should be attributed to physical dissolution. At the same time, we can also reasonably postulate that the amount of physically dissolved CO_2 (3.8%) in a 10 wt% chitin/IL solution is equal to that in a 10 wt% chitosan/IL solution under the same conditions. From Fig. 2, curves a and b, we find that the highest CO_2 sorption capacity of 10 wt% chitosan/IL is almost equal to the amount of the physically dissolved CO_2 added to the theoretical chemically bound CO_2 (4.5%), which further illustrates that almost all the amino groups in the chitosan/IL solution (which have higher activity) participate in this CO_2 capturing and releasing process. In addition, the sorption rates of these solutions are fast, and it only takes 180 minutes for chitosan/IL solution to reach 98% sorption capacity, and for chitin/IL solution to reach 95% sorption capacity under the same conditions.

Reversibility of CO_2 fixation by these systems was also examined. Taking the 10 wt% chitosan/IL solution as an example, the CO_2 was reduced to a 1.4% level in 30 minutes at 100 °C, and was completely released under vacuum. After releasing CO_2 completely, the ionic liquid solution was cooled to 30 °C and used directly in subsequent fixation/release cycles (see Fig. 2, curve a, between 360 minutes and 690 minutes).

Conclusions

In summary, chitin and chitosan are biologically renewable, biodegradable, biocompatible, almost non-toxic, and biofunctional. Therefore, it is important to use these biopolymers for the benefit of all life on earth as ecological and environmentally friendly materials without disturbing natural cycles. In this article, we have described a novel processing platform for chitin and chitosan using the ionic liquid [Bmim]Cl as a solvent. Although the ionic liquid can not completely disrupt the crystalline domains of chitosan and only a partially dissolved solution can be obtained, it does not affect its utilization. We have demonstrated that the chitin/IL and chitosan/IL solutions are an efficient, reversible fixing system for carbon dioxide, and the 10% wt chitosan/IL solution shows significant CO_2 sorption capacity (8.1% mol with respect to ionic liquid) under mild conditions (30 °C, 1 atm CO_2). To our knowledge, this is the first utilization of chitin and chitosan solutions for fixing CO_2. There are potential applications for CO_2 storage materials for recovering CO_2 from industrial exhaust, as well as for CO_2 gas sensing. Our present work could offer a convenient, environmentally friendly process platform and new strategies for expanding chemical modification and applications of these biorenewable polymers. New chemical modifications and applications of these natural polymers based on this processing platform are in progress.

Acknowledgements

We thank the National Basic Research Program of China (No. 2003CB615704) for financial support.

References

1 For recent reviews, see: T. Welton, *Chem. Rev.*, 1999, **99**, 2071; P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772; R. A. Sheldon, *Chem. Commun.*, 2001, 2399; J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, 3667, and references therein; R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792.

2 S. A. Forsyth, D. R. MacFarlane, R. J. Thomson and M. von Itzstein, *Chem. Commun.*, 2002, 714; R. P. Swatloski, S. K. Spear, J. D. Holbrey and R. D. Rogers, *J. Am. Chem. Soc.*, 2002, **124**, 4974; J. Wu, J. Zhang, H. Zhang, J. He, Q. Ren and M. Guo, *Biomacromolecules*, 2004, **5**, 266; H. Zhang, J. Wu, J. Zhang and J. He, *Macromolecules*, 2005, **38**, 20, 8272; D. M. Phillips, L. F. Drummy, R. R. Naik, H. C. De Long, D. M. Fox, P. C. Trulove and R. A. Mantz, *J. Mater. Chem.*, 2005, **15**, 4206; H. B. Xie, S. H. Li and S. B. Zhang, *Green Chem.*, 2005, **7**, 606; W. M. Reichert, A. E. Visser, R. P. Swatloski, S. K. Spear and R. D. Rogers, *Abstr. Papers Am. Chem. Soc.*, ACS, Washington, DC, 2001, vol. 221, U562–U562 52-IEC Part 1.

3 M. B. Turner, S. K. Spear, J. D. Holbrey and R. D. Rogers, *Biomacromolecules*, 2004, **5**, 1379; M. B. Turner, S. K. Spear, J. D. Holbrey, D. T. Daly and R. D. Rogers, *Biomacromolecules*, 2005, **6**, 2497.

4 A. B. Foster and J. M. Webber, *Adv. Carbohydr. Chem.*, 1960, **15**, 371.

5 O. C. Agboh and Y. Qin, *Polym. Adv. Technol.*, 1996, **8**, 355; S. Hirano, *Polym. Int.*, 1999, **48**, 732; D. J. Macquarrie and J. J. E. Hardy, *Ind. Eng. Chem. Res.*, 2005, **44**, 23, 8499 and references therein; J. J. E. Hardy, S. Hubert, D. J. Macquarrie and A. J. Wilson, *Green Chem.*, **6**, 53.

6 G. Kunike, *J. Soc. Dyers Colour.*, 1926, **42**, 318; E. Knecht and E. Hibbert, *J. Soc. Dyers Colour.*, 1926, **42**, 343.

7 T. Sannan, K. Kurita and Y. Iwakura, *Die Makromolekulare Chemie*, 1975, **176**, 1191.

8 P. R. Austin, *US Pat.* 3879377; R. C. Capozza and P.A. Califf, *US Pat.* 3988411; P. R. Austin, *Chem. Abstr.*, 1978, **88**, 6349d; A. Einbu, S. N. Naess, A. Elgsaeter and K. M. Varum, *Biomacromolecules*, 2004, **5**, 2048.

9 Mitsubishi Rayon Co. Ltd, *Jpn. Pat.*, 81106901; Fuji Spinning Co. Ltd, *Jpn. Pat.*, 59116418.

10 M. Weltrowski, B. Martel and M. Morcellet, *J. Appl. Polym. Sci.*, 1996, **59**, 647–654.

11 J. W. Nah and M. K. Jang, *J. Polym. Sci., Part A: Polym. Chem.*, 2002, **40**, 3796.

12 P. J. Dyson, M. C. Grossel, N. Srinivasan, T. Vine, T. Welton, D. J. Williams, A. J. P. White and T. Zigras, *J. Chem. Soc., Dalton Trans.*, 1997, 3465.

13 D. B. Dell'Amico, F. Calderazzo, L. Labella, F. Marchetti and G. Pampaloni, *Chem. Rev.*, 2003, **103**, 3857; M. H. Erin and M. R. Dmity, *Tetrahedron*, 2003, **59**, 9619; D. B. Eleanor, D. M. Rebecca, N. Ioanna and H. D. James, *J. Am. Chem. Soc.*, 2002, **124**, 926; V. Shimming, C. G. Hoelger, G. Buntkowsky, I. Sack, J. H. Fuhrhop, R. Stefano and H. H. Limbach, *J. Am. Chem. Soc.*, 1999, **121**, 4892; G. Sartori and D. W. Savage, *Ind. Eng. Chem. Fundam.*, 1983, **22**, 239, and references therein.

14 T. Yamaguchi, L. M. Boetje, C. A. Koval, R. D. Noble and C. N. Bowman, *Ind. Eng. Chem. Res.*, 1995, **34**, 4071; T. Yamaguchi, C. A. Koval, R. D. Nobel and C. Bowman, *Chem. Eng. Sci.*, 1996, **51**, 4781; E. Sada, H. Kumazawa and Z. Han, *Chem. Eng. J.*, 1985, **31**, 109; A. S. Kovvali and K. K. Sirkar, *Ind. Eng. Chem. Res.*, 2001, **40**, 2502; D. M. Rudkevich and H. Xu, *Chem. Commun.*, 2005, 2651, and references therein; E. D. Bates, R. D. Mayton, I. Ntai and J. H. Davis Jr., *J. Am. Chem. Soc.*, 2002, **124**, 926.

Size-controlled synthesis of metal oxide nanoparticles with a flow-through supercritical water method

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Received 3rd January 2006, Accepted 30th May 2006
First published as an Advance Article on the web 15th June 2006
DOI: 10.1039/b518291c

Hydrothermal synthesis of metal oxide ($AlOOH/Al_2O_3$, CuO, Fe_2O_3, NiO, ZrO_2) nanoparticles from metal nitrate aqueous solution was carried out at 673 K and pressures ranging from 25 MPa to 37.5 MPa with a flow-through supercritical water method. Size, phase and crystallinity of the obtained particles were characterized by TEM, XRD and TG, respectively. Effect of the difference of the metals in starting materials, pressures and concentrations on particle size and crystallinity was analyzed on the basis of supersaturation, which was evaluated by estimated metal oxide solubility. The result suggests that supersaturation should be set to higher than around 10^4 in this method to obtain particles under 10 nm in diameter. Further, crystallinity of the obtained particles was evaluated as weight loss through TG analysis. It was found that higher supersaturation decreased the crystallinity. This result can be explained that high supersaturation led to the inclusion of water molecules during the formation of particles.

Introduction

Metal oxide particles under 10 nm in diameter are attracting much attention in catalytic, ceramic, electrical, optical and other fields because of enhanced quantum effects.[1] Several techniques such as sol–gel,[2] spray pyrolysis,[3] thermal decomposition[4] and hydrothermal/solvothermal synthesis[5] have been proposed for producing metal oxide nanoparticles. However, these methods require long reaction times and use organic solvents, which made additional processes necessary for the complete synthesis process.

Over the past ten years, a flow-through supercritical water method (FT-SCW) for continuous hydrothermal synthesis has been established for forming micro- or nanosized metal oxide fine particles in supercritical water.[6] In this method, an aqueous solution of starting materials is pressurized and fed into a mixing tee that combines reactants with preheated water. Rapidly heating results from the mixing, which allows the hydrothermal reactions to take place continuously. When water in its near-critical or supercritical state is used, the hydrothermal reaction rate and metal oxide solubility can be greatly varied since the reaction solvent properties are strongly dependent on thermodynamic conditions in these regions.[7] Therefore, the FT-SCW method can be used to possibly change size, morphology, and crystal structure of many types of particles. Generally, at pressures close to the critical pressure of waer (22.1 MPa), the reaction rate of hydrothermal synthesis above the critical temperature of water (T_C = 647 K) is a few orders of magnitude higher than that at temperatures below T_C.[7] In contrast, metal oxide solubilities above T_C are a few orders of magnitude lower than that under T_C.[8] Thus, this FT-SCW method has great potential for producing nanosized metal oxide fine particles.[7,9] There are few reports that demonstrate the controllability of the particle size on the basis of metal oxide solubility and supersaturation.

In this work, to develop the FT-SCW method as a generic technology for producing nanocrystals, we focus on the determination of the experimental conditions for producing metal oxide nanoparticles under 10 nm in diameter by the FT-SCW method of various particle sizes including their crystallinity on the basis of estimated metal oxide solubilities.

Experimental

Solutions were prepared by dissolving precise amounts of metal nitrates ($Al(NO_3)_3{\cdot}9H_2O$, $Cu(NO_3)_3{\cdot}3H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, $ZrO(NO_3)_2{\cdot}2H_2O$, Wako Pure Chemicals, Osaka, Japan) and potassium hydroxide (KOH, Wako Pure Chemicals, Osaka, Japan) crystals in distilled and deionized water (resistivity > 0.18 MΩ m). The concentrations of the metal nitrates were from 0.005 and 0.5 mol kg^{-1} as feed solutions.

A schematic diagram of the experimental flow apparatus is shown in Fig. 1. Metal nitrate aqueous solution was fed with a pump 1 at a flow rate of 20 g min^{-1}. The solution was mixed at mixing point with preheated water fed with a pump 2 at a flow

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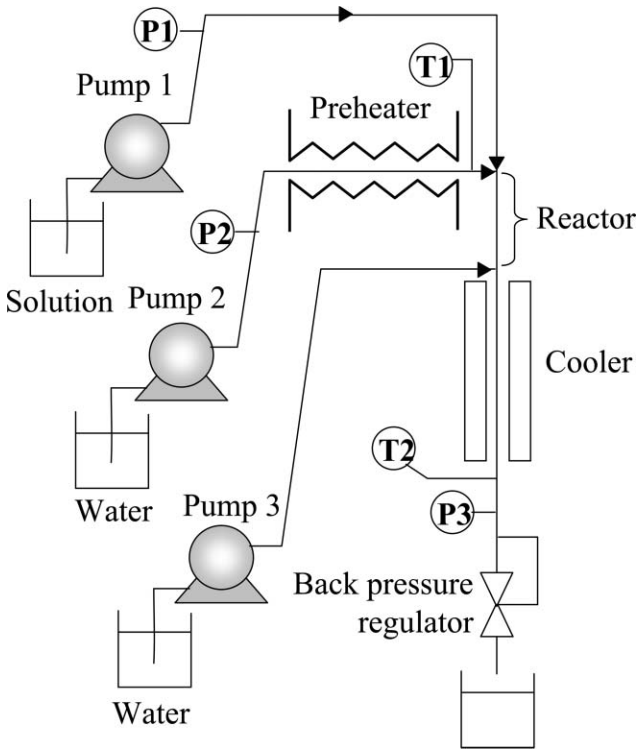


Fig. 1 A schematic diagram of flow-through experimental apparatus.

rate of 80 g min^{-1} and then the mixture was rapidly heated to the reaction temperature by the micro-mixing unit (id 0.3 mm). The reactor was made of SUS316 tube (id 1.6 mm). Reaction temperature was calculated on the basis of enthalpy balance with enthalpy of water, flow rate and temperature of each solution at given conditions. Residence time, τ, was calculated using eqn (1):

$$\tau = \frac{V}{F(\rho_{298}/\rho_{673})} \quad (1)$$

where F is the total flow rate and V is the reactor volume. ρ_{298} and ρ_{673} are the densities of pure water at 298 K and 673 K at the given pressures, respectively. At the exit of the reactor, the fluid was quenched by mixing cooling water directly into the reacting stream with a pump 3 at a flow rate of 100 g min^{-1} and by an external water jacket. The fluctuation of the system pressure was maintained within 0.1 MPa by using a back pressure regulator that was placed after the cooler. Particles were recoverd as a slurry solution and removed using a membrane filter, washed with pure water, and dried at 333 K in an electric oven for 24 h.

Table 1 Equilibrium reactions for $Ni(NO_3)_2 + H_2O$ system

[1] $NiO(s) + 2H^+ \rightleftharpoons Ni^{2+} + H_2O$	$K_1 = \frac{[Ni^{2+}]\gamma_{z=2}}{[H^+]^2\gamma_{z=1}^2}$
[2] $NiO(s) + H^+ \rightleftharpoons NiOH^+$	$K_2 = \frac{[NiOH^+]}{[H^+]}$
[3] $NiO(s) + H_2O \rightleftharpoons Ni(OH)_2{}^0$	$K_3 = [Ni(OH)_2{}^0]$
[4] $NiO(s) + 2H_2O \rightleftharpoons Ni(OH)_3{}^- + H^+$	$K_4 = [Ni(OH)_3{}^-][H^+]\gamma_{z=1}^2$
[5] $Ni^{2+} + NO_3{}^- \rightleftharpoons NiNO_3{}^+$	$K_5 = \frac{[NiNO_3^+]}{[Ni^{2+}][NO_3^-]\gamma_{z=2}}$
[6] $NiNO_3{}^+ + NO_3{}^- \rightleftharpoons Ni(NO_3)_2{}^0$	$K_6 = \frac{[Ni(NO_3)_2^0]}{[NiNO_3^+][NO_3^-]\gamma_{z=1}^2}$
[7] $HNO_3{}^0 \rightleftharpoons H^+ + NO_3{}^-$	$K_7 = \frac{[H^+][NO_3^-]\gamma_{z=1}^2}{[HNO_3^0]}$
[8] $H_2O \rightleftharpoons H^+ + OH^-$	$K_8 = [H^+][OH^-]\gamma_{z=1}^2$

The crystal structure of the products was analyzed by powder X-ray diffractometry (XRD, RINT-2200, Rigaku), using Cu Kα radiation. Observation of these products was performed by transmission electron microscopy (TEM, TECNAI-G2, FEI Co.). Particle size distribution and average particle size with standard deviation (S.D.) were determined on the basis of the diameter of about 200 particles measured from TEM results. Weight of water included in the obtained precipitates was measured by thermal gravimetric analysis (TG) (TG/DTA220, Seiko Inst. Inc.). Weight loss was defined as follows:

$$X = \left(1 - \frac{W}{W_0}\right) \times 100 \quad (2)$$

Table 2 Experimental conditions and results

Starting materials	Pressure/ MPa	Nitrate concentration/ mol kg^{-1}	KOH concentration/ mol kg^{-1}	Crystal phase	Conversion (%)	Average size (S.D.)/nm	Crystallite size/nm	Crystallite size after TG/nm	Weight loss (%)	Solubility/ mol kg^{-1}	Supersaturation (—)
$Al(NO_3)_3$	30	0.01	0	AlO(OH)	96.7	5.6 (0.6)	10.8	—	23.65	2.5×10^{-7}	4.0×10^{4}
				Al_2O_3			4.4	4.9			
$Cu(NO_3)_2$	30	0.01	0	CuO	49.5	30.9 (15.5)	27.3	36.8	0.63	5.8×10^{-4}	1.6×10^{1}
$Fe(NO_3)_3$	25	0.01	0	Fe_2O_3	98.9	5.1 (1.7)	—	—	4.81	7.1×10^{-11}	1.4×10^{8}
$Fe(NO_3)_3$	30	0.01	0	Fe_2O_3	98.3	5.5 (1.4)	5.8	25.1	5.74	4.2×10^{-10}	2.4×10^{7}
$Fe(NO_3)_3$	37.5	0.01	0	Fe_2O_3	98.8	5.5 (1.5)	—	—	5.93	1.4×10^{-9}	7.3×10^{6}
$Fe(NO_3)_3$	30	0.001	0	Fe_2O_3	94.4	6.1 (1.5)	—	—	4.17	4.1×10^{-10}	2.4×10^{6}
$Fe(NO_3)_3$	30	0.05	0	Fe_2O_3	99.2	8.2 (5.7)	—	—	4.56	4.3×10^{-10}	1.2×10^{8}
$Fe(NO_3)_3$	25	0.1	0	Fe_2O_3	99.2	6.6 (2.5)	—	—	4.77	6.9×10^{-11}	1.4×10^{9}
$Ni(NO_3)_2$	30	0.01	0	NiO	69.2	16.7 (8.5)	22.6	26.4	1.96	2.3×10^{-5}	4.4×10^{2}
$Ni(NO_3)_2$	30	0.01	0.0175	NiO	89.5	6.1 (2.8)	—	—	—	9.9×10^{-7}	1.0×10^{4}
$Ni(NO_3)_2$	30	0.01	0.02	NiO	90.9	3.4 (0.8)	4.3	24.2	9.00	5.7×10^{-10}	1.8×10^{7}
$ZrO(NO_3)_2$	30	0.001	0	ZrO_2	97.0	4.3 (1.1)	—	—	4.97	2.7×10^{-18}	3.7×10^{14}
$ZrO(NO_3)_2$	30	0.01	0	ZrO_2	99.8	4.3 (1.0)	4.7	5.2	6.50	2.1×10^{-16}	4.7×10^{13}
$ZrO(NO_3)_2$	30	0.05	0	ZrO_2	99.9	4.6 (0.9)	—	—	6.45	6.6×10^{-15}	7.6×10^{12}
$ZrO(NO_3)_2$	30	0.1	0	ZrO_2	100.0	4.7 (1.1)	—	—	6.70	3.4×10^{-14}	2.9×10^{12}

where W and W_0 are particle weights after holding the temperature at 873 K and 373 K, respectively. The concentration of the remaining metal ions in the recovered aqueous solutions was measured by inductively coupled plasma (ICP) emission spectroscopy (SPS-7800, Seiko). Conversion of metal ions into solid product was defined as follows:

$$Y = \left(1 - \frac{C}{C_0}\right) \times 100 \quad (3)$$

where C and C_0 are molal concentrations of the metal species in the recovered and feed solutions, respectively.

Estimation of metal oxide solubilities

To study hydrothermal crystallization, information on the solubility of the formed crystalline substances and identification of the ionic species are essential. As examples, equilibrium reactions that should be considered for the $Ni(NO_3)_2 + H_2O$ system are shown in Table 1. The concentration of dissolved species can be estimated by solving the system of nonlinear equations of equilibrium constants shown in Table 1, mass balance relations for Ni and NO_3, charge balance relation, and formulation for the ion activity coefficients.[10] The activity coefficients of neutral aqueous species and the activity of water were assumed to be unity because of the dilute aqueous conditions. The dissociation constants of HNO_3 and H_2O at 673 K and 30 MPa were calculated from the literature data by Chlistunoff *et al.*[11] and Marshall and Franck,[12] respectively. The dissolution constants of metal oxides and the association reactions of metal cations and NO_3^- were calculated on the basis of revised HKF equation of state.[13] Here, since conditions were lower than 50 MPa at 673 K, which is outside of the high prediction accuracy region of the model, we adopted the following method. Considering that the HKF equation of state can provide reliable predictions in the high density region, the equilibrium constants at 673 K and pressured ranging from 100 to 500 MPa (densities from 0.693 to 0.933 g cm^{-3}) were calculated. Then the equilibrium constants at the higher density conditions were correlated with an empirical function of water density, $\log_{10} K = a + b \log_{10}\rho$, where a and b were fitted to the data at 673 K for each reaction.[14] This function has been widely used for correlating density dependence of equilibrium constants at given temperature at supercritical condition.[14] Finally, the equilibrium constants at the experimental condition were estimated with the equation. The metal oxide solubility is defined as the total concentration of the metal ion aqueous complex species.

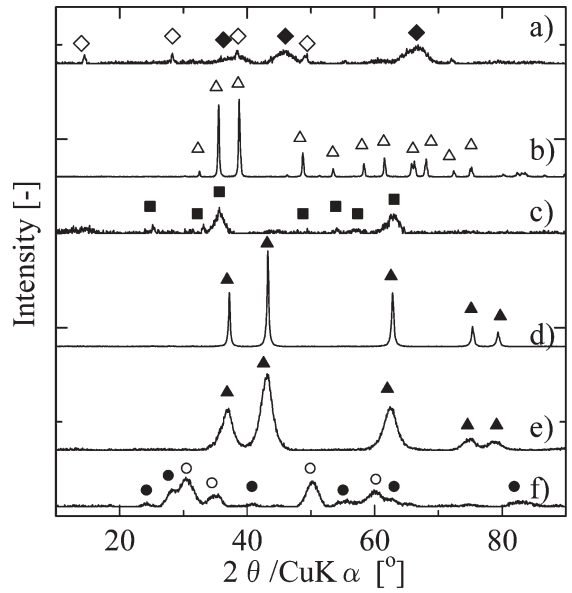
As widely known, supersaturation, σ, is the driving force for precipitation and it is defined by the following relation:

$$\sigma = \frac{S_0 - S}{S} \quad (4)$$

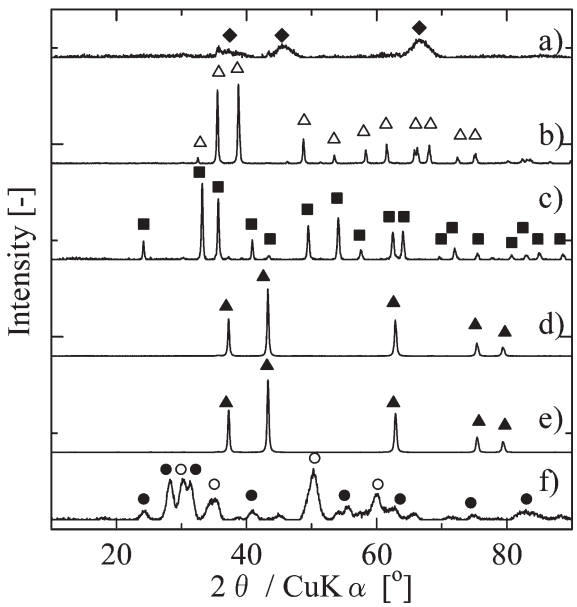
where S and S_0 denote estimated metal oxide solubility at 673 K and metal concentration of the starting solutions, respectively.

Results and discussion

Experimental conditions and results are summarized in Table 2. Typical XRD results of the obtained particles are shown in Fig. 2. All peaks of the obtained crystals from $Al(NO_3)_3$, $Cu(NO_3)_2$, $Fe(NO_3)_3$, $Ni(NO_3)_2$, and $ZrO(NO_3)_2$ were assigned to $AlO(OH)/Al_2O_3$, CuO, Fe_2O_3, NiO, and ZrO_2, respectively. Typical TEM results of the obtained crystals are shown in Fig. 3. Nanoparticles with sizes less than around 50 nm could be produced. The addition of KOH decreased the average particle size of NiO from 17 to 3 nm. As shown in Table 2, the average particle size from TEM showed



(1) before TG analysis



(2) after TG analysis

Fig. 2 XRD patterns of the obtained crystals from 0.01 mol kg^{-1} nitrate solution at 673 K and 30 MPa. (a) $Al(NO_3)_3$, (b) $Cu(NO_3)_2$, (c) $Fe(NO_3)_3$, (d) $Ni(NO_3)_2$, (e) $Ni(NO_3)_2$ + KOH, (f) $ZrO(NO_3)_2$; open rhombus: AlO(OH), closed rhombus: Al_2O_3, open triangle: CuO, closed square: Fe_2O_3, closed triangle: NiO, open circle: ZrO_2 (orthorhombic), closed circle: ZrO_2 (monoclinic).

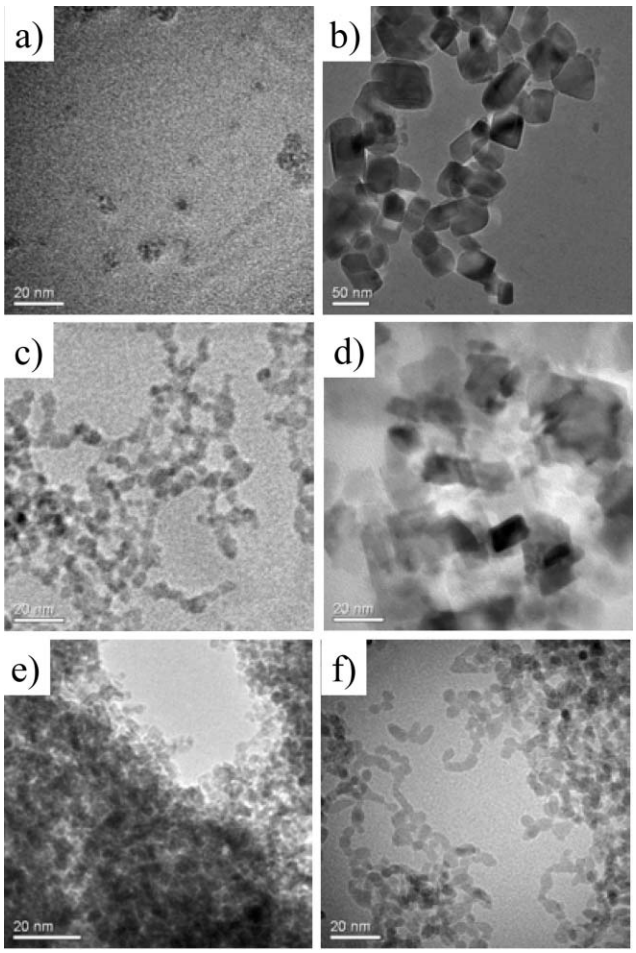


Fig. 3 TEM images of the obtained crystals from 0.01 mol kg^{-1} nitrate solution at 673 K and 30 MPa. (a) $Al(NO_3)_3$, (b) $Cu(NO_3)_2$, (c) $Fe(NO_3)_3$, (d) $Ni(NO_3)_2$, (e) $Ni(NO_3)_2$ + 0.02 mol kg^{-1} KOH, (f) $ZrO(NO_3)_2$.

good agreement with the crystallite size from XRD and this comfirmed that the obtained particles were single crystal. Fig. 4 shows typical TG result for Fe_2O_3. Weight change was defined as the difference between the steady state values at 373 K and 673 K. CuO exhibited the highest crystallinity and in contrast,

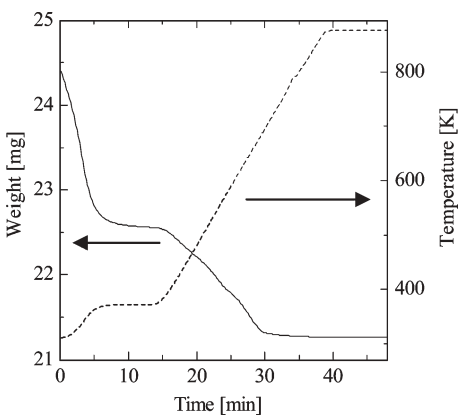


Fig. 4 TG curve of the obtained crystals from 0.01 mol kg^{-1} $Fe(NO_3)_3$ at 673 K and 30 MPa.

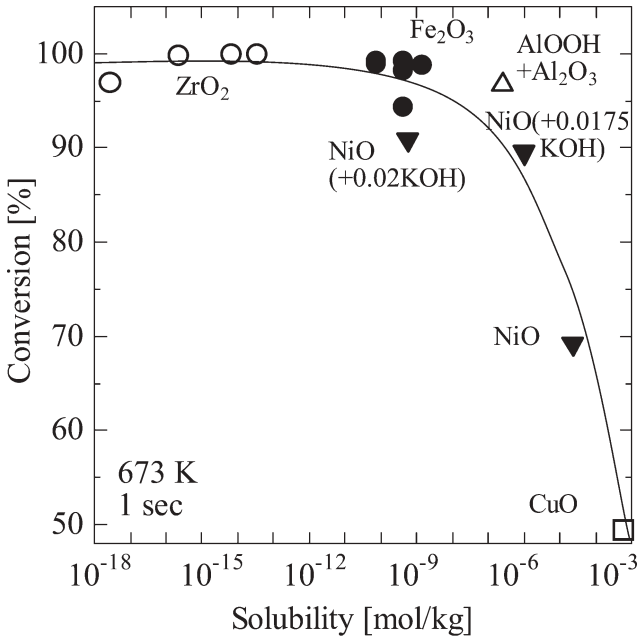


Fig. 5 Conversion as a function of metal oxide solubility.

ZrO_2 showed the lowest crystallinity. Further, XRD patterns of products after the TG analysis, namely calcination treatment, are also shown in Fig. 2. From the ICP analysis, the CuO system showed the lowest conversion and in contrast ZrO_2 showed the highest conversion.

In the following section, the effects of starting materials and conditions on conversion, particle size, and crystallinity were analyzed on the basis of metal oxide solubility and supersaturation. The relationship between the conversion and the metal oxide solubility is shown in Fig. 5 (the line is an eye guide). As the solubility decreased, the conversion increased

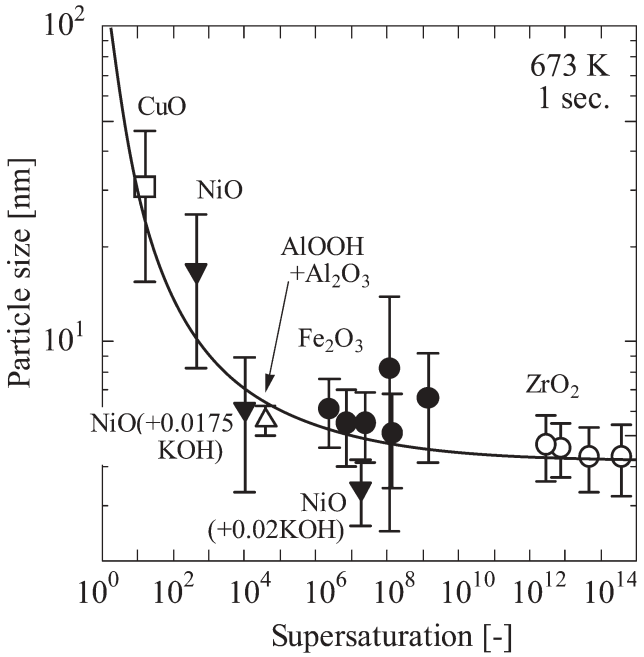


Fig. 6 Average particle size as a function of supersaturation.

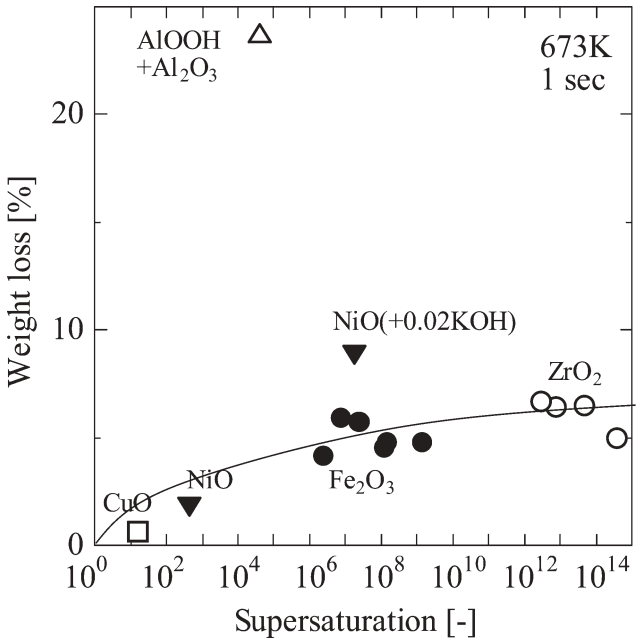


Fig. 7 Weight loss as a function of supersaturation.

in the order: ZrO_2 > Fe_2O_3 > $AlOOH/Al_2O_3$ > NiO > CuO. Namely, the solubility strongly depended on the precipitation rate. The relationship between the average particle size and the supersaturation is shown in Fig. 6 (the line is an eye guide). As widely known in nucleation theory, the average particle size tends to decrease with increasing supersaturation. It was found that supersaturation higher than a factor of about 10^4 was needed to obtain particles under 10 nm in diameter at the conditions shown in Table 1 and Fig. 6. As described in the previous paragraph, addition of KOH tended to cause the particle size to decrease(Fig. 6), which can be attributed to the decrease in solubility. The relationship between crystallinity (weight loss) and the supersaturation is shown in Fig. 7 (the line is an eye guide). The condition of high supersaturation means that the driving force for precipitation is large and during this non-steady precipitation process, water molecules are easily occluded in precipitates. As a result, low crystalline solids can be produced. In contrast, small supersaturation generally leads to slower precipitation and, during this period, relatively stable intermediate species are probably formed. For these differences, it was assumed that the crystallinity increased with decreasing supersaturation. In the case of the products from $Al(NO_3)_3$, the weight loss showed significantly higher values and this is assumed to be the phase transition from AlO(OH) to Al_2O_3 on the basis of the XRD pattern in Fig. 2.

Conclusions

Metal oxide nanoparticles of $AlO(OH)/Al_2O_3$, CuO, Fe_2O_3, NiO, ZrO_2 could be synthesized with a flow-through supercritical water method. The size, conversion, and crystallinity of the obtained particles were analyzed on the basis of estimated metal oxide solubility and supersaturation at the given conditions. As a result, condition for obtaining nanoparticles under 10 nm in diameter was determined to be higher than a supersaturation factor of around 10^4 at 673 K. The result of this work promises a great advantage of the FT-SCW method for size-controlled synthesis of metal oxide nanoparticles.

Acknowledgements

This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for scientific research and for promotion of multi-disciplinary research projects and by the Industrial Technology Research Grant Program in 02A44001d from New Energy and the Industrial Technology Development Organization (NEDO) of Japan. We also thank Mr Hideki Matsumoto, and Prof. Mikio Konno, Department of Chemical Engineering, Tohoku University, for their assistance in the thermal analyses.

References

1 S. Somiya and R. Roy, *Bull. Mater. Sci.*, 2000, **23**, 453.
2 G.-h. Ning, X.-p. Zhao and J. Li, *Opt. Mater.*, 2004, **27**, 1.
3 S. B. Park and Y. C. Kang, *J. Aerosol Sci.*, 1997, **28**, S473.
4 Y. Yang, H. Chen, B. Zhao and X. Bao, *J. Cryst. Growth*, 2004, **263**, 447.
5 A. A. Ismail, A. El-Midany, E. A. Abdel-Aal and H. El-Shall, *Mater. Lett.*, 2005, **59**, 1924.
6 K. Sue, K. Murata, K. Kimura and K. Arai, *Green Chem.*, 2003, **5**, 659.
7 T. Adschiri, Y. Hakuta, K. Sue and K. Arai, *J. Nanopart. Res.*, 2001, **3**, 227.
8 K. Sue, Y. Hakuta, R. L. Smith, Jr., T. Adschiri and K. Arai, *J. Chem. Eng. Data*, 1999, **44**, 1422.
9 E. Reverchon and R. Adami, *J. Supercrit. Fluids*, 2005, **37**, 1.
10 S. N. Lvov, X. Y. Zhou and D. D. Macdonald, *J. Electroanal. Chem.*, 1999, **463**, 146.
11 J. Chlistunoff, K. J. Ziegler, L. Lasdon and K. P. Johnston, *J. Phys. Chem. A*, 1999, **103**, 1678.
12 W. L. Marshall and E. U. Franck, *J. Phys. Chem. Ref. Data*, 1981, **10**, 295.
13 H. C. Helgeson, D. H. Kirkham and G. C. Flowers, *Am. J. Sci.*, 1981, **281**, 1249.
14 P. C. Ho, D. A. Palmer and R. H. Wood, *J. Phys. Chem. B*, 200, **104**, 12084.

Preparation, characterization and application of amino acid-based green ionic liquids

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Received 18th January 2006, Accepted 30th May 2006
First published as an Advance Article on the web 16th June 2006
DOI: 10.1039/b600813e

A family of novel ionic liquids with amino acids and their derivatives as cations and environmentally benign materials as anions have been synthesized using easy preparation techniques. The ionic liquids obtained have the same characteristics as conventional imidazolium ionic liquids and the same chiralities as natural amino acids. Thermal stabilities, phase behaviour, viscosities and miscibilities of the representative family members have been investigated, generally showing no difference from conventional ionic liquids. These amino acid ionic liquids may be used as catalysts and "fully green" solvents in the cycloaddition of cyclopentadiene to methyl acrylate, which is a typical Diels–Alder reaction. This approach to treating amino acids and their derivatives can serve as an alternative to traditional ionic liquids having synthetic chemical components.

Introduction

Ionic liquids are a class of liquids comprised entirely of ions. The term was introduced in order to distinguish them from classical molten salts in view of their low melting points, usually below 100 °C.[1] A somewhat arbitrary 100 °C dividing line between the melting points of materials described as ionic liquids and those called molten salts has been widely accepted because the former materials are versatile replacements for traditional aqueous and organic solvents. Typical formulations of ionic liquids rely mostly on quaternary nitrogen cations such as alkylammonium, dialkylimidazolium and alkylpyridinium, and anions such as Cl^-, $AlCl_4^-$, PF_6^-, BF_4^-, $N(CF_3SO_2)_2^-$, $CF_3CO_2^-$ and $CF_3SO_3^-$. Salts drawn from this pool, ranging from water-sensitive to hydrophilic, have shown attractive chemistry and great potential related to their ionic nature, which confers non-volatility, high thermal stability, unique miscibility and a wide electrochemical window.[2–4] Since the end of the last century, an increasing volume of literatures describing the syntheses and applications of novel ionic liquids has appeared.[5–7] The term "task-specific ionic liquids" or "functionalized ionic liquids" has become a fashionable description of such materials, and indicates an attempt to capitalize on the potential "design" capacity of ionic liquids and make them true working systems rather than merely novel media.[8–14]

Many advanced materials, based on novel findings and concepts, have been developed recently. So it is pertinent to ask why ionic liquids, which are not new, have stimulated such broad interest in both academia and industry over the past five years, and have had an impact in almost all areas of chemistry and materials science. The reason for their success is related to environmental concerns, and stimulated by their bright commercial future.[15,16] Recently, ionic liquids have been widely considered as greener alternatives to volatile organic solvents mainly due to their negligble vapour pressure; but if measured against the 12 principles of green chemistry, whether ionic liquids themselves can be claimed as "green" solvents is still open to debate.[17] Commonly used ionic liquids, for example, based on imidazolium cations and fluorinated anions are synthetic chemicals, and therefore are not as green as desired. The chloroaluminate ionic liquids are air- and water-sensitive. The hexafluorophosphate ionic liquids are even unstable towards hydrolysis, potentially releasing HF when in contact with moisture.[18] Though these ionic liquids cannot enter the environment by evaporation, most of them are water-soluble and could easily enter the biosphere this way.[19] In order to obtain "fully green" ionic liquids, the starting materials must be at least non-toxic, whilst for a perfect solution, they should be renewable. Moreover, development of new "green" ionic liquids still requires relatively low cost and easy preparation. Biorenewable natural compounds are ideal materials from the viewpoints of both environmental and economical concerns.[20] A few successful samples have been reported, for example, using lactates,[21,22] sugar substitutes[23,24] and amino acids[25] to prepare anions, and sugars[26] and amino acids[27–29] to prepare cations, of which several are potentially chiral ions.

Unlike classical molten salts, which are inorganic in nature, ionic liquids are organic–inorganic multi-component materials whose chemical (polarity/acidity/coordination ability/solubility) and physical (fluidity/conductivity/transferability/liquidus range) properties can be tailored by modifying/changing the type of cations, modifying the alkyl substituents in the cations, or modifying/changing the type and the composition of the anions. Ionic liquids are designable materials. In evaluating any successful work concerning the preparation of ionic liquids from natural materials, we have emphasized in our previous communication that the "designer solvent" properties of ionic

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liquids should be maintained, *i.e.*, the physical/chemical properties of the ionic liquids obtained can be adjusted by changing the side-chain attached to the main group, and even the natural properties of the materials should be completely retained.[30]

Recently, we have reported two families of a new generation of ionic liquid cations directly derived from natural α-amino acids and their ester salts.[30] Here we mainly report two types of "fully green" ionic liquids, [AAE]NO_3 **2** and [AAE]Sac **3**, of which the cations involved are directly derived from natural α-amino acid ester salts, and the anions involved are non-toxic inorganic or organic anions. A special "fully green" ionic liquid, ProNO_3 **1**, is also involved. (Fig. 1) This paper is the first investigation, to our knowledge, into the preparation of "fully green" ionic liquids, in which both the cations and anions are from non-toxic renewable materials. Studies on the physical and chemical properties of these "fully green" ionic liquids show that these ionic liquids possess similar characteristics to conventional ionic liquids, and can be used as catalysts and solvents to catalyze Diels–Alder reaction.

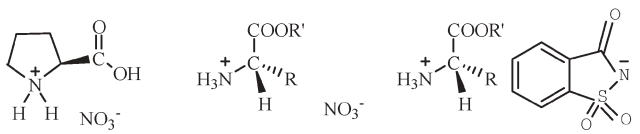
Results and discussion

Synthesis

Amino acids and their derivatives are the biggest natural pool of chemicals containing quarternary nitrogens. However, few of them have been directly used to prepare the ammonium cations of ionic liquids. We have shown how amino acids and amino acid ester hydrochlorides can be converted to ionic liquid cations.[30] Two families of cations, *i.e.* [AA] (amino acid) and [AAE] (amino acid ester), have been obtained. In principle, combination of these cations with environmentally benign anions may make "fully green" ionic liquids possible. Moreover, the choice of [AAE] cations will not only decrease the melting points of the products[30] but also increase biodegradability, because of the incorporation of an ester group.[31] Regarding the anions, NO_3^- and Sac^- (saccharide) are the best; NO_3^- is a non-toxic, pharmaceutically acceptable inorganic anion,[18] while Sac^- is non-fluorous and has well-established toxicological profiles.[32]

ProNO_3 is an ideal fully green ionic liquid. The synthesis involves acidification of proline with nitric acid, which is an atom-economic reaction, and water is the reaction medium. ProNO_3 is, to our knowledge, the only room temperature free-flowing liquid in the family of [AA]X ionic liquids, due to its particular tetrahydropyrrole ring.[30]

Based on multiple considerations, including cheap green material sources, low melting points, and the ability to vary the ester group functionality *etc.*, we have focused on [AAE]NO_3 and [AAE]Sac as the strong candidates for green ionic liquids.



1 ProNO_3 **2** [AAE]NO_3 **3** [AAE]Sac

Fig. 1 Structures of the amino acid-based fully green ionic liquids.

The synthesis of [AAE]NO_3 ionic liquids requires separately dissolving [AAE]Cl and $AgNO_3$ in methanol. Then, after mixing these two solutions, filtering and evaporating the resulting liquid *in vacuo*, the product [AAE]NO_3 was obtained. The [AAE]Sac ionic liquids were synthesized by the reaction of sodium saccharin and [AAE]Cl in acetone. The resultant precipitate of sodium chloride was filtered off and acetone was evaporated. Since [AAE]Cl can be obtained commercially, the preparation of both [AAE]NO_3 and [AAE]Sac ionic liquids is a one-step high-yield reaction without any poisonous by-product. Furthermore, it is worthy to note that the esterification provides a possibility of adjusting the properties of the ionic liquids obtained. Twenty natural amino acids provide a wide choice for the framework of the ionic liquids. Alcohols with different carbon numbers or functional groups can be appended to the ester to modulate the properties of the ionic liquids.

Physicochemical properties

ProNO_3 is easy to decompose, and the decomposition temperature is only 138 °C. The [AAE]NO_3 and [AAE]Sac ionic liquids obtained are thermally stable from about 150 to 230 °C under N_2 (Table 1). Different amino acid cations affect the decomposition temperatures because the cations are less stable than anions in this case. PheC_1NO_3 began to decompose at 224 °C, mainly due to its relatively stable benzene ring structure. As a whole, [AAE]Sac ionic liquids have better thermal stability than the corresponding [AAE]NO_3 ionic liquids. When these ionic liquids are rapidly heated to 250 °C in air, an irritative odour resulted and a very small amount of black residue remained. However, they are thermally stable enough to fit the 100 °C decomposition temperature criterion described by Wasserscheid for chiral ionic liquids.[29]

It is clear from Table 1 that more than half of the products (14 out of 20) are room temperature ionic liquids, and almost all of the products are ionic liquids below 100 °C. ProNO_3, [AAE]NO_3 and [AAE]Sac ionic liquids have the same glass state character as that of conventional ionic liquids. The glass transition temperatures are determined by differential scanning calorimetry (DSC) from the first heating cycle, after initially cooling samples to between −70 and −100 °C. All of them have a glass transition temperature (T_g) between 0 and −70 °C. Then, as the temperature increases, the solid samples indicate clear melting peaks at melting points (T_m) on the DSC curves. The DSC curves of some solid samples, AlaC_1NO_3 (T_m 61 °C), ValC_1NO_3 (T_m 74 °C), and LeuC_1NO_3 (T_m 75 °C), are given in Fig. 2. The room temperature liquid samples show a different picture, however. The DSC curves of IleC_1NO_3, ProC_1NO_3, AlaC_1Sac, ThrC_1Sac, and ProC_1Sac as liquid samples (Fig. 2) display two steps. They more likely have two glass transition temperatures, rather than one glass transition temperature and one melting point. As the temperature increases, they give solid–solid transitions at lower temperatures and solid–liquid transitions at higher temperatures. Because there is no absorbing peak relative to T_m observed in liquid samples, IleC_1NO_3 was examined as an example. When it was cooled with dry ice and acetone bath to −70 °C, it became a hard and transparent solid. When warmed to near

Table 1 The properties of amino acid ester nitrates ([AAE]NO_3) and amino acid ester saccharins ([AAE]Sac)

No.	Ionic liquids	T_m/°C	T_g/°C	T_{dec}/°C (±5%)	$[\alpha]_D^{20}/10^{-1}$ deg cm^2 g^{-1}	[AAE]Cl $[\alpha]_D^{20}/10^{-1}$ deg cm^2 g^{-1}	Viscosity/cP (±3%)
1	$ProNO_3$	−18[a]	−45[b]	138	−27.1	−84.0[c]	5140 (30 °C)
2	$GlyC_1NO_3$	44	−26	178	—	—	92 (70 °C)
3	$AlaC_1NO_3$	61	−34	186	+6.2	+6.2	104 (80 °C)
4	$ValC_1NO_3$	74	−33	195	+22.5	+22.3	445 (80 °C)
5	$LeuC_1NO_3$	75	−31	210	+15.4	+17.6	1550 (80 °C)
6	$IleC_1NO_3$	−14[a]	−36[b]	172	+32.7	+37.8	—
7	$PheC_1NO_3$	92	−32	224	+21.1	+18.1	—
8	$ThrC_1NO_3$	−12[a]	−32[b]	156	−9.5	−9.4	—
9	$SerC_1NO_3$	105	−30	179	+7.3	+3.7	—
10	$ProC_1NO_3$	−16[a]	−67[b]	159	−36.4	−34.5	186 (30 °C)
11	$ProC_2NO_3$	−17[a]	−50[b]	183	−30.9	−36.4	213 (30 °C)
12	$ProC_3NO_3$	6[a]	−71[b]	208	−32.4	−36.0	398 (30 °C)
13	$ProC_4NO_3$	−11[a]	−70[b]	163	−31.9	−35.9	275 (30 °C)
14	$AlaC_1Sac$	−14[a]	−27[b]	184	+2.2	+6.2	1390 (80 °C)
15	$ValC_1Sac$	−16[a]	−29[b]	185	+9.4	+22.3	3040 (80 °C)
16	$LeuC_1Sac$	7[a]	−1[b]	223	+6.1	+17.6	1050 (80 °C)
17	$IleC_1Sac$	7[a]	−8[b]	177	+11.5	+37.8	14 500 (80 °C)
18	$ThrC_1Sac$	−1[a]	−9[b]	200	−4.3	−9.4	55 900 (80 °C)
19	$ProC_1Sac$	−19[a]	−29[b]	190	−20.7	−34.5	3320 (80 °C)
20	$ProC_2Sac$	8[a]	−42[b]	212	−22.6	−36.4	3020 (50 °C)

[a] No melting transition observed or solid–liquid transition temperature. [b] Solid–solid transition temperature. [c] Specific rotation value of proline.

−35 °C, it became a very viscous opaque solid, then, near −15 °C, it became a transparent liquid. During this procedure, $IleC_1NO_3$ absorbed heat continually just like a glass state material. Furthermore, different anions affect the melting points and phase transition temperatures clearly. [AAE]Sac ionic liquids have a higher glass transition temperatures than the corresponding [AAE]NO_3 ionic liquids. The introduction of Sac^- blurs the melting points of the ionic liquids. All the $ProNO_3$, [AAE]NO_3 and [AAE]Sac ionic liquids readily form long-lived supercooled phases.

Table 1 also gives viscosity data for $ProNO_3$, some [AAE]NO_3 and [AAE]Sac ionic liquids when they are in liquid state. From these data it can be concluded that [AAE]NO_3 ionic liquids display qualitatively similar viscosity behaviour to conventional imidazolium ionic liquids.[33] On the other hand, [AAE]Sac ionic liquids are very viscous liquids, due to the saccharin anion.[23] The viscosities of many ionic liquids are strongly dependent upon temperature.[4] With modest heating, the viscosities of [AAE]Sac ionic liquids decrease rapidly. A typical case is that the viscosity of $ProC_1Sac$ decreases from 173 000 cP at 50 °C to 108 00 cP at 70 °C, and then to only 3320 cP at 80 °C. A consistent downtrend is also found in $ProC_2Sac$, whose viscosity decreases from 29 700 cP at 30 °C to 7990 cP at 40 °C, and then 3020 cP at 50 °C. So it is possible to obtain a comparatively low viscosity green ionic liquid when heating to a temperature higher than the phase transition temperature. All of these viscosity data were determined using a rotational viscometer. There are no obvious changes on viscosity observed when the angular speed of the rotating cylinder changes. Therefore, it is suggested that all of the $ProNO_3$, [AAE]NO_3 and [AAE]Sac are Newtonian fluids just like conventional ionic liquids.[4]

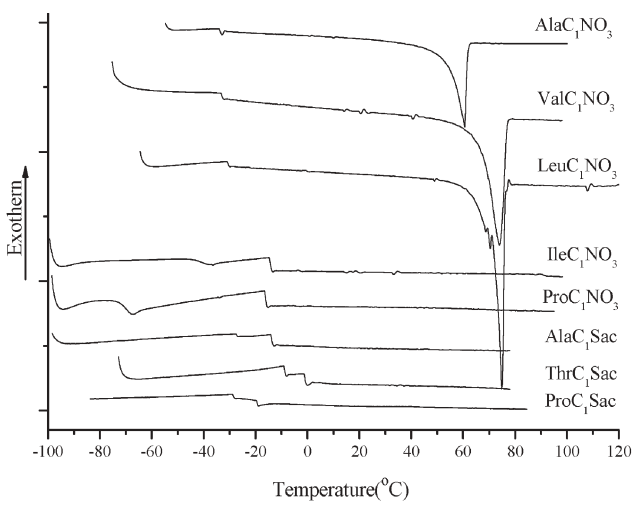


Fig. 2 Differential scanning calorimetry curves of some typical amino acid ionic liquids [AAE]NO_3 and [AAE]Sac.

It is very significant to this work that the stereogenic centers in the synthetic precursors, amino acids or amino acid esters, are still retained in the ionic liquids. Some stereogenic centers of chiral ionic liquids have been reported to undergo racemization after a certain amount of time.[34] In Table 1, the specific rotations, in degrees, of the ionic liquids have been compared with those of the corresponding synthetic precursors, L-proline or [L-AAE]Cl. It can be proved that most of the [AAE]NO_3 ionic liquids have nearly the same specific rotation values as their precursors. However, the specific rotation values of [AAE]Sac ionic liquids decrease slightly. This phenomenon may be explained by an optical dilution effect of the Sac anion on a formula unit basis. A similar result is found for $ProNO_3$; the presence of the anion makes the specific rotation value decrease, compared to L-proline. Furthermore, continuous observation indicates that the chiralities of all the samples shown in Table 1 remain the same, even for over three months, demonstrating that [AAE]-type ionic liquids offer a new family of easily prepared chiral ionic liquids.

Table 2 ^{1}H-NMR Chemical shifts (relative to TMS) of $-NH_3^+$ of amino acid ionic liquids ($ProNO_3$ and $[AAE]NO_3$), in d_6-DMSO

Ionic liquid	$-NH_3^+$(δ/ppm)
$ProNO_3$	9.490, 8.832[a]
$GlyC_1NO_3$	8.321
$AlaC_1NO_3$	8.320
$ValC_1NO_3$	8.566
$LeuC_1NO_3$	8.479
$IleC_1NO_3$	8.545
$PheC_1NO_3$	8.449
$ThrC_1NO_3$	8.343
$SerC_1NO_3$	8.387
$ProC_1NO_3$	9.759, 9.122[a]
$ProC_2NO_3$	9.569, 9.041[a]
$ProC_3NO_3$	9.697, 9.040[a]
$ProC_4NO_3$	9.386[a]

[a] $-NH_2-^+$.

Each amino acid ionic liquid has two or three active hydrogens. The pH value of $AlaC_1NO_3$, obtained from a 1 mol L^{-1} water solution, as an example of an $[AAE]NO_3$ ionic liquid, is 3.5, showing weak Brønsted acidity. The acidity is believed to come from the hydrogen connected with the quaternary nitrogen. The ^{1}H-NMR chemical shifts of $-NH_3^+$ (or $-NH_2-^+$) of $ProNO_3$ and $[AAE]NO_3$ ionic liquids are shown in Table 2. The broad peaks of the RNH_3^+ hydrogens above 8.3 ppm indicate that $[AAE]NO_3$ ionic liquids have certain acidities. The shifts of proline ionic liquids are higher than 9.0 ppm, which is very different to other $[AAE]NO_3$ ionic liquids. This shows that the peculiar tetrahydropyrrole ring of proline enhances the ability of N–H to form hydrogen bonds. The amino acid structure of other $[AAE]NO_3$ salts has little influence on their acidities. Significantly, the acidity of amino acid ionic liquids will be used in many green acidic catalysis processes in future.

Ionic liquids are environmentally benign solvents in many reactions. It was important for us to investigate the miscibility of them with some conventional solvents. All of the investigated $ProNO_3$, $[AAE]NO_3$ and [AAE]Sac ionic liquids are miscible with high polarity solvents such as water, low molecular weight alcohols and ketones. (Table 3) Amino acid structure and alkyl chain length have no strong influence in these cases. The miscibility of [AAE] ionic liquids with water cannot be affected by anions even if the anion is hydrophobic (PF_6^- or NTf_2^-), reflecting the presence of the strong H-bonding ability of the cation. $[AAE]NO_3$ and [AAE]Sac ionic liquids are immiscible with non-polar alkanes, benzene, and diethyl ether. Ethyl acetate and chloroform appear to constitute the borderline. Some of the $[AAE]NO_3$ ionic liquids such as $ValC_1NO_3$ and $ProC_1NO_3$ are partly miscible with chloroform and immiscible with ethyl acetate. Some of the [AAE]Sac ionic liquids are miscible with ethyl acetate and immiscible with chloroform, owing to the amide of the saccharin enhancing the miscibility based on the principle of "like dissolves like". Furthermore, $ProC_1$Sac and $ProC_2$Sac are partly miscible with chloroform, maybe due to the peculiar tetrahydropyrrole of proline.

Amino acid ionic liquid-catalyzed Diels–Alder reaction

The Diels–Alder reaction is one of the most important carbon–carbon bond forming reactions used to synthesize six-membered ring structures.[35] The cycloaddition of cyclopentadiene to methyl acrylate (Fig. 3) was carried out in [AAE] ionic liquids for 24 h at room temperature without any organic solvents (Table 4). In [AAE] ionic liquids, the stereoselectivities are at the same level (*endo*/*exo* around 3 to 4) just like those obtained in $[C_4mim]BF_4$ ionic liquid[36] (Entry 1, 2). The increment of the amount of [AAE] from 30 mol% to 100 mol% produces a small enhancement of the *endo*/*exo* ratio (Entry 3, 4, 8, 9). [AAE]Sac ionic liquids have better stereoselectivity than $[AAE]NO_3$ ionic liquids (Entry 8, 9). Catalysis activity is also found in $AlaC_1NO_3$ (Entry 10). But the enantiomeric excesses of *endo* and *exo* products are found to be less than 3%,

Table 3 Miscibility with other solvents of amino acid ionic liquids ($ProNO_3$, $[AAE]NO_3$ and [AAE]Sac)[a]

Ionic liquids	Water	Ethanol	Acetone	Ethyl acetate	Chloroform	Ether	Benzene	n-Hexane
$ProNO_3$	m	m	m	i	i	i	i	i
$GlyC_1NO_3$	m	m	m	i	i	i	i	i
$AlaC_1NO_3$	m	m	m	i	i	i	i	i
$ValC_1NO_3$	m	m	m	i	p	i	i	i
$LeuC_1NO_3$	m	m	m	i	i	i	i	i
$IleC_1NO_3$	m	m	m	i	i	i	i	i
$PheC_1NO_3$	m	m	m	i	i	i	i	i
$ThrC_1NO_3$	m	m	m	i	i	i	i	i
$SerC_1NO_3$	m	m	m	i	i	i	i	i
$ProC_1NO_3$	m	m	m	i	p	i	i	i
$ProC_2NO_3$	m	m	m	i	p	i	i	i
$ProC_3NO_3$	m	m	m	i	p	i	i	i
$ProC_4NO_3$	m	m	m	i	p	i	i	i
$AlaC_1$Sac	m	m	m	i	i	i	i	i
$ValC_1$Sac	m	m	m	p	i	i	i	i
$LeuC_1$Sac	m	m	m	p	i	i	i	i
$IleC_1$Sac	m	m	m	p	i	i	i	i
$ThrC_1$Sac	m	m	m	p	i	i	i	i
$ProC_1$Sac	m	m	m	i	p	i	i	i
$ProC_2$Sac	m	m	m	i	p	i	i	i

[a] m: miscible, p: partly miscible, i: immiscible.

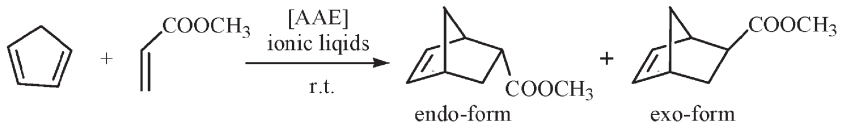


Fig. 3 Diels–Alder reactions catalyzed by amino acid ionic liquids.

by chiral GC analysis. These results are consistent with those in chiral [bmim]lactate ionic liquid[21] and chiral *N*,*N*-di(2′*S*-2-methylbutyl)imidazolium bromide ionic liquid.[37] The great degree of hydrogen-bonding interactions were thought to decrease the enantioselectivity,[21] but the small steric requirements of methyl acrylate are considered to be the primary reason.

Conclusions

The combination of amino acid cations with suitable environmentally benign anions for the preparation of "fully green" ionic liquids has been carried out. The easy preparation makes the commercialization of the processes based on amino acid-based ionic liquids immediately available. These amino acid-based ionic liquids have the same characteristics as conventional ionic liquids. Most importantly, they are derived from non-toxic, even natural, materials. They are also functionalized ionic liquids with both acidity and chirality. These ionic liquids may play a role in many catalysed reactions, such as the Diels–Alder reaction, as substitutes for volatile organic solvents to make the system greener.

Experimental

General methods

All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. Methanol, ethanol, acetone, and ethyl ether were purified by standard procedures.[38] L-Amino acid ester hydrochlorides (L-[AAE]Cl) were purchased or prepared from reference methods.[39] The NMR spectra were recorded in d_6-DMSO or d_6-acetone on a Varian 300 MHz instrument, with TMS as the internal standard. Secondary ion mass spectrometry (SIMS) was performed on an APEXII FT-ICR mass spectrograph. Glass transition temperatures (T_g) and melting points (T_m) from the onset position were determined from the first heating cycle, after initially cooling samples to between −70 and −100 °C. T_g and T_m were recorded on a Thermal Analysis DSC2010 differential scanning calorimeter with heating at 2 °C min^{-1} under nitrogen. Decomposition temperatures (T_{dec}) were determined with a Thermal Analysis SDT2960 simultaneous differential thermal analyzer with a heating rate of 5 °C min^{-1} under nitrogen. Specific rotation values of the ionic liquids in solution in CH_3OH (c = 2) were obtained with a Model 341LC polarimeter. Viscosities were determined on a Thermo Haake RheoStress 300 rotational viscometer. GC analyses were carried out on an Agilent Chrompack HP-6820 equipped with a capillary column (30 m × 0.25 mm, using nitrogen as carrier gas).

Table 4 Diels–Alder reactions catalyzed by amino acid ionic liquids ([AAE]NO_3 and [AAE]Sac).

Entry	Ionic liquid	Catalyst (mol%)	Yield (%)	*endo*/*exo*
1	$[C_4mim]BF_4$	30	98	3.3
2	$[C_4mim]BF_4$	100	95	3.5
3	$ProC_1NO_3$	30	96	3.1
4	$ProC_1NO_3$	100	99	3.7
5	$ProC_2NO_3$	30	95	3.3
6	$ProC_3NO_3$	30	98	3.3
7	$ProC_4NO_3$	30	97	3.3
8	$ProC_1Sac$	30	89	3.3
9	$ProC_1Sac$	100	87	3.9
10	$AlaC_1NO_3$	30	97	3.8

Preparation of L-proline nitrate (L-ProNO$_3$). 11.51 g (0.10 mol) of L-proline was dissolved in 20 mL water. An equal number of moles of nitric acid (3 mol L^{-1}) was added to the solution. The reaction mixture was then warmed to 60 °C for 24 h. After evaporating *in vacuo* at 60 °C, 17.81 g of the light yellow transparent liquid L-$ProNO_3$ was obtained. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 9.49 (s, 1H, NH_2), 8.83 (s, 1H, NH_2), 4.33 (t, J = 7.2 Hz, 1H, CH), 3.23 (m, 2H, CH_2), 2.27 (m, 1H, CH_2), 1.95 (m, 3H, CH_2, CH_2) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 170.50, 58.95, 45.58, 27.94, 23.24 ppm. *m*/*z* (SIMS, positive ion) 116.0706 [$C_5H_{10}NO_2^+$]. *m*/*z* (SIMS, negative ion) 61.9884 [NO_3^-].

General procedure for preparation of [AAE]NO$_3$. 0.020 mol of L-[AAE]Cl and 0.020 mol of $AgNO_3$ were separately dissolved in methanol. After mixing the two solutions and filtering the precipitate, the resulting liquid was evaporated *in vacuo* at 60 °C. The product was purified from methanol–ether until no Ag^+ salt remained. After drying *in vacuo* for at least 24 h, the product L-[AAE]NO_3 was obtained.

Glycine methyl ester nitrate (GlyC$_1$NO$_3$). 2.51 g (0.020 mol) of $GlyC_1Cl$ and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product $GlyC_1NO_3$ was obtained as a colourless transparent liquid, and crystallized to a white solid after three days. Yield: 88%. ^{1}H-NMR δ (300MHz, d_6-DMSO): 8.32 (s, 3H, NH_3), 3.86 (s, 2H, CH_2), 3.74 (s, 3H, CH_3) ppm. ^{13}C-NMR δ (75MHz, d_6-DMSO): 168.20, 52.61, 39.80 ppm. *m*/*z* (SIMS, positive ion) 90.0549 [$C_3H_8NO_2^+$]. *m*/*z* (SIMS, negative ion) 61.9883 [NO_3^-].

L-Alanine methyl ester nitrate (L-AlaC$_1$NO$_3$). 2.79 g (0.020 mol) of L-$AlaC_1Cl$ and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-$AlaC_1NO_3$ was obtained as a colourless transparent liquid, and crystallized to a white solid after one week. Yield: 93%. ^{1}H-NMR δ (300 MHz, d_6-DMSO):

8.32 (s, 3H, NH_3), 4.13 (q, J = 7.2 Hz, 1H, CH), 3.76 (s, 3H, CH_3), 1.39 (d, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 170.39, 52.84, 47.90, 15.69 ppm. *m/z* (SIMS, positive ion) 104.0706 [$C_4H_{10}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Valine methyl ester nitrate (L-ValC_1NO_3). 3.35 g (0.020 mol) of L-ValC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-ValC_1NO_3 was obtained as a colourless transparent liquid, and crystallized to a white solid after one day. Yield: 84%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 8.57 (s, 3H, NH_3), 3.88 (d, J = 2.7 Hz, 1H, CH), 3.76 (s, 3H, CH_3), 2.17 (m, 1H, CH), 0.99 (d, J = 6.9 Hz, 3H, CH_3), 0.94 (d, J = 6.9 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 169.30, 57.36, 52.63, 29.38, 18.38, 17.57 ppm. *m/z* (SIMS, positive ion) 132.1017 [$C_6H_{14}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9883 [NO_3^-].

L-Leucine methyl ester nitrate (L-LeuC_1NO_3). 3.63 g (0.020 mol) of L-LeuC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-LeuC_1NO_3 was obtained as a colourless transparent liquid, and crystallized to a white solid after one week. Yield: 87%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 8.48 (s, 3H, NH_3), 4.02 (t, J = 6.9 Hz, 1H, CH), 3.76 (s, 3H, CH_3), 1.58–1.77 (m, 3H, CH_2, CH), 0.90 (d, J = 6.3 Hz, 6H, CH_3, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 170.38, 52.92, 50.56, 23.82, 22.12, 22.07 ppm. *m/z* (SIMS, positive ion) 146.1175 [$C_7H_{16}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9883 [NO_3^-].

L-Isoleucine methyl ester nitrate (L-IleC_1NO_3). 3.63 g (0.020 mol) of L-IleC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-IleC_1NO_3 was obtained as a colourless transparent viscous liquid. Yield: 79%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 8.55 (s, 3H, NH_3), 3.91 (d, J = 3.9 Hz, 1H, CH), 3.75 (s, 3H, CH_3), 1.93 (m, 1H, CH), 1.23–1.53 (m, 2H, CH_2), 0.93 (d, J = 6.9 Hz, 3H, CH_3), 0.89 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 170.44, 56.58, 52.82, 36.22, 25.48, 14.63, 11.82 ppm. *m/z* (SIMS, positive ion) 146.1175 [$C_7H_{16}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Phenylalanine methyl ester nitrate (L-PheC_1NO_3). 4.31 g (0.020 mol) of L-PheC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-PheC_1NO_3 was obtained as a white solid. Yield: 83%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 8.45 (s, 3H, NH_3), 7.21–7.37 (m, 5H, Ph), 4.33 (t, J = 6.6Hz, 1H, CH), 3.67 (s, 3H, CH_3), 3.08 (d, J = 6.6 Hz, 2H, CH_2) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 169.44, 134.51, 129.37, 128.68, 127.36, 53.28, 52.67, 36.05 ppm. *m/z* (SIMS, positive ion) 180.1020 [$C_{10}H_{14}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Threonine methyl ester nitrate (L-ThrC_1NO_3). 3.39 g (0.020 mol) of L-ThrC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-ThrC_1NO_3 was obtained as a colourless transparent viscous liquid. Yield: 85%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 8.34 (s, 3H, NH_3), 4.15 (m, 1H, CH), 3.95 (d, J = 4.2 Hz, 1H, CH), 3.75 (s, 3H, CH_3), 1.20 (d, J = 6.9 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 168.91, 65.21, 58.23, 53.08, 20.13 ppm. *m/z* (SIMS, positive ion) 134.0811 [$C_5H_{12}NO_3^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Serine methyl ester nitrate (L-SerC_1NO_3). 3.11 g (0.020 mol) of L-SerC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-SerC_1NO_3 was obtained as a colourless transparent liquid, and then crystallized to a white solid. Yield: 89%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 8.39 (s, 3H, NH_3), 5.58 (s, 1H, OH), 4.16 (t, J = 3.3 Hz, 1H, CH), 3.83 (d, J = 3.3 Hz, 2H, CH_2), 3.76(s, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 168.52, 59.47, 54.26, 52.84 ppm. *m/z* (SIMS, positive ion) 120.0656 [$C_4H_{10}NO_3^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Proline methyl ester nitrate (L-ProC_1NO_3). 3.31 g (0.020 mol) of L-ProC_1Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-ProC_1NO_3 was obtained as a light yellow transparent liquid. Yield: 88%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 9.76 (s, 1H, NH_2), 9.12 (s, 1H, NH_2), 4.46 (m, 1H, CH), 3.77 (s, 3H, CH_3), 3.28 (m, 2H, CH_2), 2.25–2.36 (m, 1H, CH_2), 1.92–2.07 (m, 3H, CH_2, CH_2) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 169.42, 58.94, 53.26, 45.75, 27.85, 23.28 ppm. *m/z* (SIMS, positive ion) 130.0862 [$C_6H_{12}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Proline ethyl ester nitrate (L-ProC_2NO_3). 3.59 g (0.020 mol) of L-ProC_2Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-ProC_2NO_3 was obtained as a light yellow transparent liquid. Yield: 90%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 9.57 (s, 1H, NH_2), 9.04 (s, 1H, NH_2), 4.43 (m, 1H, CH), 4.23 (q, J = 7.2 Hz, 2H, CH_2), 3.27 (m, 2H, CH_2), 2.25–2.35 (m, 1H, CH_2), 1.89–2.06 (m, 3H, CH_2, CH_2), 1.25 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 168.93, 62.25, 59.02, 45.78, 27.89, 23.22, 14.00 ppm. *m/z* (SIMS, positive ion) 144.1019 [$C_7H_{14}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Proline propyl ester nitrate (L-ProC_3NO_3). 3.87 g (0.020 mol) of L-ProC_3Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-ProC_3NO_3 was obtained as a light yellow transparent liquid. Yield: 87%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 9.70 (s, 1H, NH_2), 9.04 (s, 1H, NH_2), 4.44 (m, 1H, CH), 4.14 (m, 2H, CH_2), 3.27 (m, 2H, CH_2), 2.25–2.36 (m, 1H, CH_2), 1.89–2.06 (m, 3H, CH_2, CH_2), 0.91 (t, J = 7.5 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-DMSO): 168.92, 62.51, 58.86, 45.53, 27.92, 23.17, 21.51, 10.27 ppm. *m/z* (SIMS, positive ion) 158.1174 [$C_8H_{16}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

L-Proline butyl ester nitrate (L-ProC_4NO_3). 4.15 g (0.020 mol) of L-ProC_4Cl and 3.40 g (0.020 mol) of $AgNO_3$ were used, and the product L-ProC_4NO_3 was obtained as a light yellow transparent liquid. Yield: 89%. ^{1}H-NMR δ (300 MHz, d_6-DMSO): 9.39 (s, 2H, NH_2), 4.45 (m, 1H, CH), 4.19 (m, 2H, CH_2), 3.26 (m, 2H, CH_2), 2.28–2.35 (m, 1H, CH_2), 1.91–2.09 (m, 3H, CH_2, CH_2), 1.64 (m, 2H, CH_2), 1.36 (m, 2H, CH_2), 0.90 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ

(75 MHz, d_6-DMSO): 168.92, 65.77, 59.01, 45.69, 30.09, 27.89, 23.17, 18.62, 13.62 ppm. *m/z* (SIMS, positive ion) 172.1330 [$C_9H_{18}NO_2^+$]. *m/z* (SIMS, negative ion) 61.9884 [NO_3^-].

General procedure for preparation of [AAE]Sac. 0.020 mol of L-[AAE]Cl and 0.030 mol of sodium saccharin (NaSac) were added to 30 mL acetone, and stirred for 24 h at room temperature. After leaching the precipitate, the liquid obtained was evaporated *in vacuo* at 80 °C. After drying *in vacuo* for at least 24 h, the product L-[AAE]Sac was obtained.

L-Alanine methyl ester saccharinate (L-AlaC$_1$Sac). 2.79 g (0.020 mol) of L-AlaC$_1$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-AlaC$_1$Sac was obtained as a light yellow transparent viscous liquid. Yield: 89%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.68–7.81 (m, 4H, Ph), 4.45 (q, J = 7.2 Hz, 1H, CH), 3.79 (s, 3H, CH_3), 1.69 (d, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-acetone): 169.98, 169.44, 144.53, 133.29, 131.88, 131.66, 122.94, 119.33, 52.32, 48.58, 15.04 ppm. *m/z* (SIMS, positive ion) 104.0706 [$C_4H_{10}NO_2^+$]. *m/z* (SIMS, negative ion) 181.9917 [$C_7H_4NO_3S^-$].

L-Valine methyl ester saccharinate (L-ValC$_1$Sac). 3.35 g (0.020 mol) of L-ValC$_1$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-ValC$_1$Sac was obtained as a light yellow transparent viscous liquid. Yield: 79%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.68–7.82 (m, 4H, Ph), 4.27 (d, J = 4.5 Hz, 1H, CH), 3.81 (s, 3H, CH_3), 2.42–2.52 (m, 1H, CH), 1.12 (dd, J = 7.2, 7.2 Hz, 6H, CH_3, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-acetone): 169.07, 168.68, 144.19, 132.92, 131.81, 131.62, 122.84, 119.21, 57.77, 51.97, 29.18, 17.46, 16.76 ppm. *m/z* (SIMS, positive ion) 132.1018 [$C_6H_{14}NO_2^+$]. *m/z* (SIMS, negative ion) 181.9918 [$C_7H_4NO_3S^-$].

L-Leucine methyl ester saccharinate (L-LeuC$_1$Sac). 3.63 g (0.020 mol) of L-LeuC$_1$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-LeuC$_1$Sac was obtained as a light yellow transparent viscous liquid. Yield: 87%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.68–7.81 (m, 4H, Ph), 4.35 (t, J = 6.9 Hz, 1H, CH), 3.81 (s, 3H, CH_3), 1.86–1.98 (m, 3H, CH, CH_2), 0.96 (d, J = 6.0 Hz, 6H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-acetone): 170.00, 169.27, 144.65, 133.35, 131.89, 131.72, 122.99, 119.39, 52.30, 51.21, 39.11, 24.01, 21.36 ppm. *m/z* (SIMS, positive ion) 146.1175 [$C_7H_{16}NO_2^+$]. *m/z* (SIMS, negative ion) 181.9917 [$C_7H_4NO_3S^-$].

L-Isoleucine methyl ester saccharinate (L-IleC$_1$Sac). 3.63 g (0.020 mol) of L-IleC$_1$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-IleC$_1$Sac was obtained as a light yellow transparent viscous liquid. Yield: 78%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.68–7.84 (m, 4H, Ph), 4.41 (d, J = 3.9 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 2.26 (m, 1H, CH), 1.39–1.68 (m, 2H, CH_2), 1.07 (d, J = 6.9 Hz, 3H, CH_3), 0.94 (t, J = 7.2 Hz, 6H, CH_3) ppm. ^{13}C-NMR δ (75MHz, d_6-acetone): 169.27, 168.83, 144.56, 132.97, 132.58, 132.54, 123.59, 119.96, 57.26, 52.51, 36.47, 25.96, 14.12, 11.29 ppm. *m/z* (SIMS, positive ion) 146.1175 [$C_7H_{16}NO_2^+$]. *m/z* (SIMS, negative ion) 181.9918 [$C_7H_4NO_3S^-$].

L-Threonine methyl ester saccharinate (L-ThrC$_1$Sac). 3.39 g (0.020 mol) of L-ThrC$_1$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-ThrC$_1$Sac was obtained as a light yellow transparent viscous liquid. Yield: 69%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.80–7.93 (m, 4H, Ph), 4.37–4.45 (m, 1H, CH), 4.27 (d, J = 4.5 Hz, 1H, CH), 3.83 (s, 3H, CH_3), 1.43 (d, J = 6.6 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-acetone): 169.02, 166.32, 143.50, 133.83, 133.50, 131.56, 124.32, 120.59, 76.40, 66.21, 52.69, 19.53 ppm. *m/z* (SIMS, positive ion) 134.0811 [$C_5H_{12}NO_3^+$]. *m/z* (SIMS, negative ion) 181.9917 [$C_7H_4NO_3S^-$].

L-Proline methyl ester saccharinate (L-ProC$_1$Sac). 3.31 g (0.020 mol) of L-ProC$_1$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-ProC$_1$Sac was obtained as a yellow transparent viscous liquid. Yield: 92%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.69–7.85 (m, 4H, Ph), 4.76 (t, J = 6.9 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 3.64 (m, 2H, CH_2), 2.45–2.57 (m, 1H, CH_2), 2.10–2.30 (m, 3H, CH_2, CH_2) ppm. ^{13}C-NMR δ (75 MHz, d_6-acetone): 168.98, 167.89, 143.53, 132.18, 132.02, 131.93, 122.96, 119.28, 58.66, 52.36, 45.43, 27.72, 22.96 ppm. *m/z* (SIMS, positive ion) 130.0862 [$C_6H_{12}NO_2^+$]. *m/z* (SIMS, negative ion) 181.9919 [$C_7H_4NO_3S^-$].

L-Proline ethyl ester saccharinate (L-ProC$_2$Sac). 3.59 g (0.020 mol) of L-ProC$_2$Cl and 6.16 g (0.030 mol) of NaSac were used, and the product L-ProC$_2$Sac was obtained as a yellow transparent viscous liquid. Yield: 88%. ^{1}H-NMR δ (300 MHz, d_6-acetone): 7.67–7.83 (m, 4H, Ph), 4.75 (t, J = 7.8 Hz, 1H, CH), 4.27 (q, J = 7.2 Hz, 2H, CH_2), 3.65 (t, J = 7.2 Hz, 2H, CH_2), 2.46–2.58 (m, 1H, CH_2), 2.09–2.31 (m, 3H, CH_2, CH_2), 1.26 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR δ (75 MHz, d_6-acetone): 168.71, 168.59, 144.05, 132.72, 131.88, 131.70, 122.87, 119.22, 61.96, 58.82, 45.49, 27.85, 23.02, 12.91 ppm. *m/z* (SIMS, positive ion) 144.1017 [$C_7H_{14}NO_2^+$]. *m/z* (SIMS, negative ion) 181.9918 [$C_7H_4NO_3S^-$].

General procedure for [AAE]X-catalyzed Diels–Alder reaction. Methyl acrylate was washed with NaOH solution and water, then dried with $CaCl_2$ and distilled prior to use. Cyclopentadiene was obtained by cracking dicyclopentadiene, distilled, and then used immediately. Ionic liquids were dried *in vacuo* before use.

In a typical Diels–Alder reaction, methyl acrylate (0.90 mL, 10.0 mmol) and cyclopentadiene (1.24 mL, 15.0 mmol) were added to the ionic liquid (3.0 mmol or 10.0 mmol) in a water bath equipped with a thermostat and stirred with a magnetic stirrer. The reaction was carried out at room temperature for 24 h under an inert atmosphere of dry nitrogen. Then the solution was extracted using diethyl ether (10 × 3 mL). The combined organic layers were evaporated to get the Diels–Alder adduct as a colourless or pale yellow transparent liquid. The *endo*/*exo* ratios and the enantiomeric excesses were determined by GC analysis.

Acknowledgements

The project was supported by a grant from the National Natural Science Foundation of China (Key Program

20533010). We thank Professor Jian-bin Huang and Dr Ke Wang at the College of Chemistry and Molecular Engineering at Peking University for the viscosity determination. We also thank Professor Bu-xing Han and Dr Xiu-min Ma at the Centre for Molecular Science at the Institute of Chemistry, Chinese Academy of Sciences for the SIMS determination.

References

1 J. D. Holbrey and K. R. Seddon, *Clean Prod. Process.*, 1999, **1**, 223.
2 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
3 P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772, *Angew. Chem.*, 2000, **112**, 3926.
4 *Ionic Liquids in Synthesis*, ed. P. Wasserscheid and T. Welton, Wiley-VCH, Weinheim, 2002.
5 D. B. Zhao, M. Wu, Y. Kou and E. Z. Min, *Catal. Today*, 2002, **74**, 157.
6 K. R. Seddon, *Nat. Mater.*, 2003, **2**, 363.
7 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792.
8 J. H. Davis, *Chem. Lett.*, 2004, **33**, 1072.
9 A. E. Visser, R. P. Swatloski, W. M. Reichert, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis and R. D. Rogers, *Chem. Commun.*, 2001, 135.
10 T. J. Geldbach and P. J. Dyson, *J. Am. Chem. Soc.*, 2004, **126**, 8114.
11 E. D. Bates, R. D. Mayton, I. Ntai and J. H. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 926.
12 D. B. Zhao, Z. F. Fei, T. J. Geldbach, R. Scopelliti and P. J. Dyson, *J. Am. Chem. Soc.*, 2004, **126**, 15876.
13 G. H. Tao, Z. Y. Chen, L. He and Y. Kou, *Chin. J. Catal.*, 2005, **26**, 253.
14 G. H. Tao, M. Zou, X. H. Wang, Z. Y. Chen, D. G. Evans and Y. Kou, *Aust. J. Chem.*, 2005, **58**, 327.
15 S. Wilkes John, *Green Chem.*, 2002, **4**, 73.
16 *Green Industrial Applications of Ionic Liquids*, ed. R. D. Rogers, K. R. Seddon and S. Volkov, Kluwer Academic, Dordrecht, 2000.
17 *Green Chemistry: Theory and Practice*, ed. P. T. Anastas and J. C. Warner, Oxford University Press, New York, 1998.
18 R. P. Swatloski, J. D. Holbrey and R. D. Rogers, *Green Chem.*, 2003, **5**, 361.
19 A. West, *Chem. World*, 2005, **2**, 32.
20 S. T. Handy, *Chem–Eur. J.*, 2003, **9**, 2938.
21 M. J. Earle, P. B. McCormac and K. R. Seddon, *Green Chem.*, 1999, **1**, 23.
22 J. Pernak, I. Goc and I. Mirska, *Green Chem.*, 2004, **6**, 323.
23 E. B. Carter, S. L. Culver, P. A. Fox, R. D. Goode, I. Ntai, M. D. Tickell, R. K. Traylor, N. W. Hoffman and J. H. Davis, *Chem. Commun.*, 2004, 630.
24 J. Pernak, F. Stefaniak and J. Weglewski, *Eur. J. Org. Chem.*, 2005, 650.
25 K. Fukumoto, M. Yoshizawa and H. Ohno, *J. Am. Chem. Soc.*, 2005, **127**, 2398.
26 S. T. Handy, M. Okello and G. Dickenson, *Org. Lett.*, 2003, **5**, 2513.
27 W. L. Bao, Z. M. Wang and Y. X. Li, *J. Org. Chem.*, 2003, **68**, 591.
28 H. Clavier, L. Boulanger, N. Audic, L. Toupet, M. Mauduit and J. C. Guillemin, *Chem. Commun.*, 2004, 1224.
29 P. Wasserscheid, A. Bösmann and C. Bolm, *Chem. Commun.*, 2002, 200.
30 G. H. Tao, L. He, N. Sun and Y. Kou, *Chem. Commun.*, 2005, 3562.
31 N. Gathergood, M. T. Garcia and P. J. Scammells, *Green Chem.*, 2004, **6**, 166.
32 *Ullman's Encyclopedia of Industrial Chemistry*, ed. G. R. von Rymon Lipinski, Wiley-VCH, Weinheim, 2003, vol. 35, p. 407.
33 K. R. Seddon, A. Stark and M. Torres, *Pure Appl. Chem.*, 2000, **72**, 2275.
34 J. J. Jodry and K. Mikami, *Tetrahedron Lett.*, 2004, **45**, 4429.
35 A. Kumar, *Chem. Rev.*, 2001, **101**, 1.
36 A. Vidiš, C. A. Ohlin, G. Laurenczy, E. Küsters, G. Sedelmeier and P. J. Dyson, *Adv. Synth. Catal.*, 2005, **347**, 266.
37 J. Howarth, K. Hanlon, D. Fayne and P. McCormac, *Tetrahedron Lett.*, 1997, **38**, 3097.
38 *Purification of laboratory chemicals*, ed. W. L. F. Armarego and D. D. Perrin, Butterworth Heinemann, Oxford, 1997.
39 R. P. Patel and S. Price, *J. Org. Chem.*, 1965, **30**, 3575.

4-Dimethylaminopyridinium carbamoylides as stable and non-hazardous substitutes of arylsulfonyl and heteroaryl isocyanates†

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Received 24th March 2006, Accepted 9th June 2006
First published as an Advance Article on the web 19th June 2006
DOI: 10.1039/b604376c

Arylsulfonyl isocyanates are commonly used for the production of arylsulfonyl carbamates and ureas, finding many commercial uses. Isocyanates are toxic and have usually been prepared using processes that require the handling of dangerous chemicals such as phosgene. Dimethylaminopyridinium carbamoylides (**3a–d** and **25**) have been designed as new, safer and non-hazardous substitutes of arylsulfonyl isocyanates and the previously unreported benzimidazol-1-yl isocyanate.

Introduction

Arylsulfonyl ureas have a wide range of practical applications such as antidiabetic[1–3] and diuretic[4] drugs, herbicides[5–8] as well as anticancer agents.[9–12] Moreover, several new potential therapeutic options have recently emerged, including the treatment of oestrogen- and androgen-dependent diseases,[13] hypertension,[14] cardiovascular, renal and pulmonary diseases[15,16] as well as *Mycobacterium tuberculosis* infections.[17]

Traditionally arylsulfonyl ureas have been prepared by methods based on hazardous irritant and moisture sensitive reagents such as arylsulfonyl isocyanates.[18–21] On the other hand, in recent years there has been increasing demand for safe and environmentally favourable methods for the syntheses of carbamates and ureas, such as processes not requiring isocyanates and halogenated reagents such as toxic phosgene or chloroformates.[22,23]

Recently, several new, safer methodologies for the preparation of arylsulfonyl ureas have been developed. For example, *N*-arylsulfonyl-*N*′-alkylureas such as *tolbutamide* and *chlorpropamide* were synthesized[24] by reacting benzenesulfonamides with *N*-alkylthiocarbonates obtained by selenium (or DMSO)-assisted carbonylation of amines with carbon monoxide and sulfur.[25,26]

Currently we are developing a project concerning the synthesis of new benzimidazole derivatives with potential application in medicine. It has been well known that benzimidazole carbamates (BZC) such as *mebendazole*, *cambendazole* or *carbendazim* of general structure **A** (Fig. 1) are important drugs for the treatment of a wide range of helminth infections.[27,28] In addition, it has been found that *carbendazim* may have a significant anticancer activity.[29] Many analogues of these compounds were synthesized and tested for their anthelmintic activity, and the results demonstrate the importance of the NH group of the benzimidazole moiety.[30,31] To explore the limits of the pharmacophore, we decided to synthesize a new class of positional isomers of BZC bearing the carbamate functionality at position 1 of the benzimidazole ring, arriving at structure **B** (Fig. 1) with a CH group in place of the weakly acidic NH group.

To achieve this goal, we noted a protocol which consists in a DMAP-catalyzed reaction of amines with di-*tert*-butyl-dicarbonate [$(Boc)_2O$] giving rise to the formation of isocyanates, which upon *in situ* trapping by an additional equivalent of amine or alcohol[32–34] provide ready access to unsymmetrical ureas and carbamates, respectively. The influence of catalyst, solvents, reaction time, stoichiometry and temperature on the products of these reactions was investigated in detail.[35] *N*,*N*′-Unsymmetrical ureas can also be synthesized through the action of lithium methylpiperazine on the *N*-Boc-protected primary amines.[36] Other methods reported for the synthesis of carbamates and ureas utilize cationic carbamoyl imidazolium salts derived from carbonyldiimidazole (CDI).[37–39]

It appears, however, that $(Boc)_2O$ and CDI applied in the above procedures must be synthesized from phosgene. Moreover, despite enormous progress made in the synthesis of aryl isocyanates and their substitutes, no attention has been paid to heterocyclic isocyanates. Therefore, we turned our attention to diphenyl carbonate (DPC), a versatile auxiliary reagent used in organic synthesis, which is prepared in bulk by oxidative carbonylation of phenol.[40,41] This led us to devise a concise and practical synthesis of 4-dimethylaminopyridinium *N*-(arylsulfonyl)carbamoylides and analogous *N*-(benzimidazol-1-yl)carbamoylide which can be regarded as a versatile synthons for the targeted arylsulfonyl (or heteroaryl) carbamates and ureas.

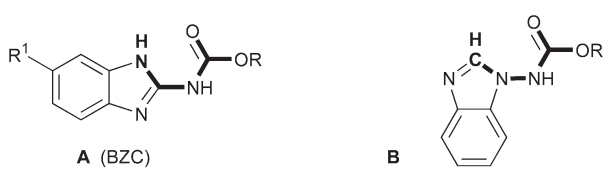

Fig. 1 The structure of benzimidazole carbamates.

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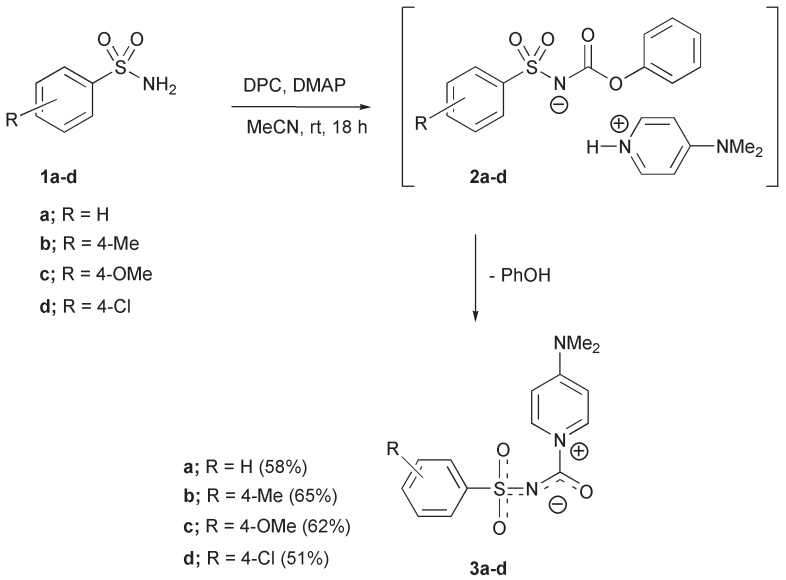
† Electronic supplementary information (ESI) available: Selected theoretical bond distances and angles, molecular diagram, and electrostatic potential maps for ylide **3a**. See DOI: 10.1039/b604376c



Scheme 1 Preparation of 4-dimethylaminopyridinium *N*-(arylsulfonyl)carbamoylides **3a–d**.

Results and discussion

As shown in Scheme 1, the reaction of benzenesulfonamides (**1a–d**, 1 molar equiv.) with diphenyl carbonate (DPC, 1.1 molar equiv.) in the presence of 4-dimethylaminopyridine (DMAP, 2 molar equiv.) carried out in acetonitrile for 18 h at room temperature led to the formation of the title 4-dimethylaminopyridinium *N*-(arylsulfonyl)carbamoylides (**3a–d**) in 51–65% yields. Product isolation is facile as the precipitated ylide can be filtered from the acetonitrile soluble phenol by-product.

Although the mechanism of this reaction has not been investigated in detail, we assume that the first step involves the replacement of the phenoxy group of DPC leading to the pyridinium salt of the corresponding carbamate (**2**). The second step consists in loss of a phenol molecule giving rise to the final product **3a–d**. In the case of *p*-chlorophenylsulfonamide (**1d**) the intermediary formed pyridinium salt **2d** could be isolated by interrupting the reaction after 6 h.

Carbamoylides **3a–d** are stable, non-hygroscopic, crystalline substances which have been stored at room temperature for at least six months with no apparent loss of activity; hence these compounds should be stable indefinitely when refrigerated. However, these compounds are relatively unstable in DMSO and proton solvents.

The results of spectral and analytical analyses were fully consistent with the proposed structure. Thus, the IR spectra of **3** showed a lack of NH stretching but the presence of C=O (1705–1710 cm^{-1}) and C=N (1645–1655 cm^{-1}) vibrations. In the ^1H NMR spectra, the N–CH_3 protons resonate as a singlet at 3.3 ppm and a pair of doublets for the pyridinium ring protons appear at 7.0 (3,5-CH) and 8.8 ppm (2,6-CH), respectively.

It should be noted that analogous pyridinium *N*-(arylsulfonyl)carbamoylides were obtained previously by reacting arylsulfonyl isocyanates with pyridine.[42,43]

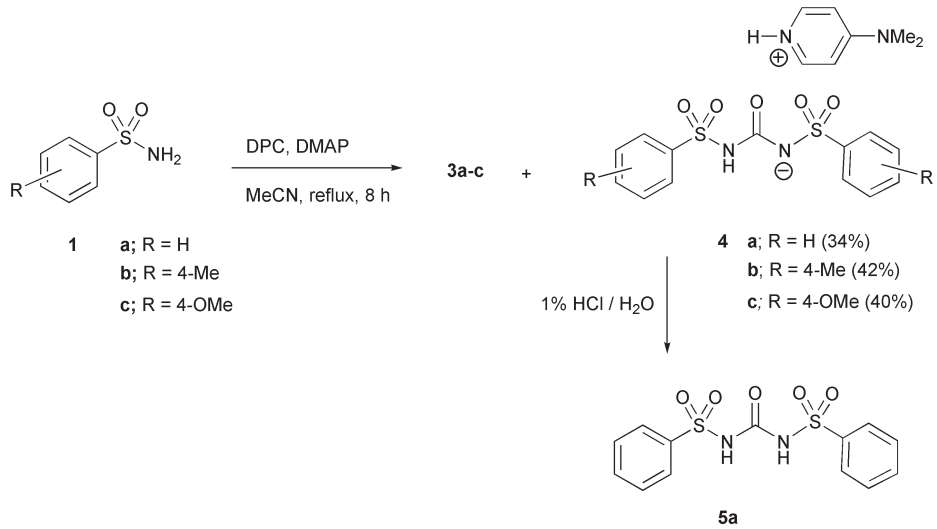
We have generated and optimized the molecular structure of the ylide **3a** using *ab initio* (RHF/6-31G**) computations. From analysis of the theoretical geometric and electronic properties of the sulfonylcarbamoyl fragment we can infer that the negative charge of the anion is extensively delocalized over both the –C(O)–N moiety and the sulfonyl group (see ESI†).

To optimize the procedure, experiments were carried out using different combinations of DPC and DMAP and two different solvents (MeCN and DMF). However, we found that the reaction of benzenesulfonamides **1a–c** (1 equiv.) with DPC (1.1 equiv.) in the presence of DMAP (1.1 equiv.) carried out in boiling acetonitrile afforded a mixture of compounds **3a–c** and pyridinium bis-(arylsulfonyl)ureates **4a–c**. Later compounds were separated by means of fractional crystallization and could be converted quantitatively into the ureas **5** by the treatment with 1% HCl (Scheme 2).

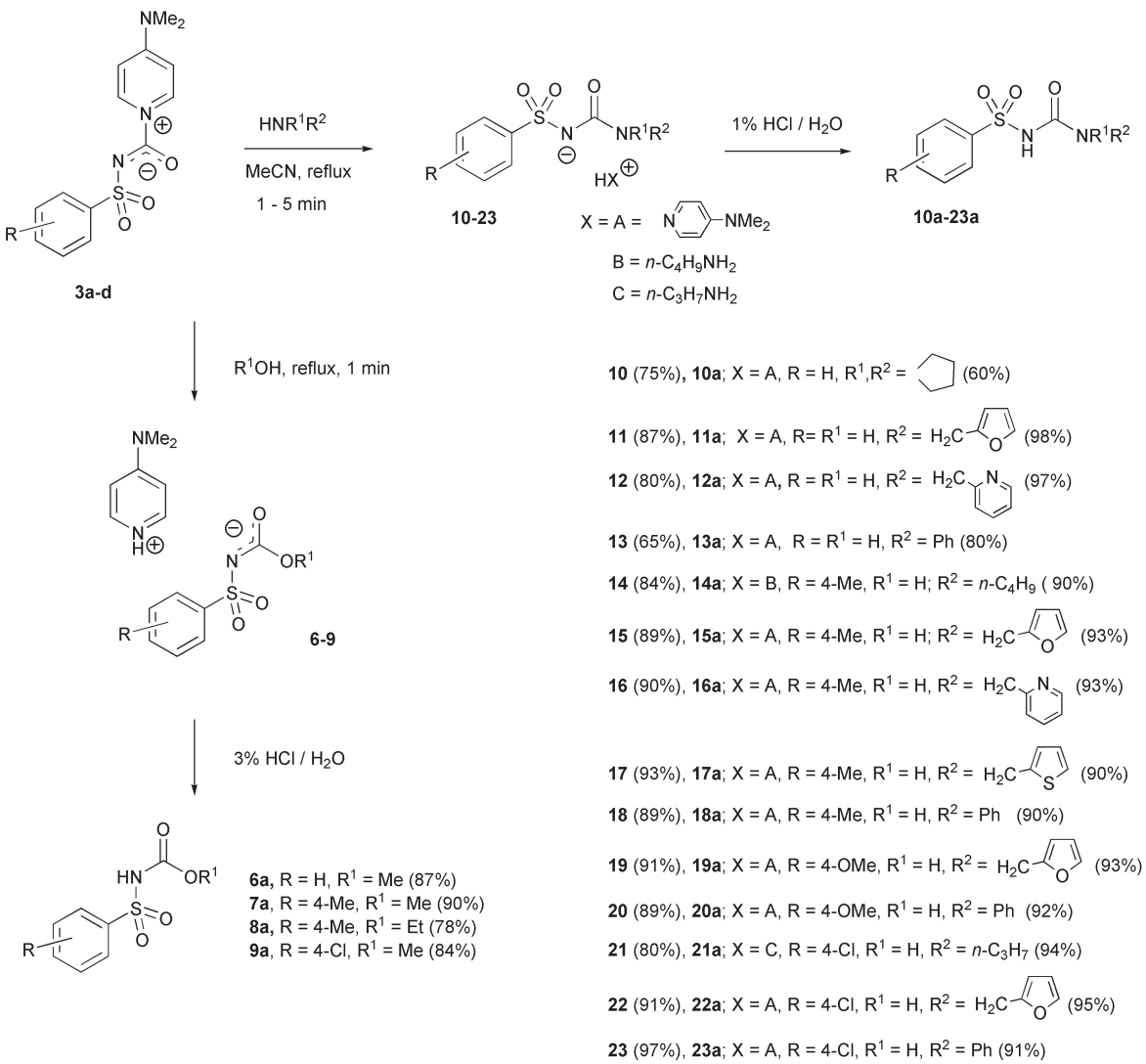
Ylides of general type **3** turned out to be valuable electrophiles for synthetic purposes. To investigate the scope of these new reagents, a series of structurally different aliphatic and aromatic amines was subjected to the reaction with **3a–d**. As illustrated in Scheme 3, the salts of unsymmetrical ureas **10–23** were generated in 65–97% yield. In a typical reaction a slight excess of the amine (in the case of propyl- and butylamine two-fold excess) was added in one portion to a solution of **3**. The reaction mixture was heated at reflux for 5–30 min and then cooled to room temperature. The product that precipitated was greater than 95% pure as evidenced by ^1H NMR and could be converted quantitatively to the corresponding urea **10a–23a**, including *tolbutamide* and *chlorpropamide*, by the treatment with 1% HCl at room temperature.

The current methodology has also been extended to prepare arylsulfonyl carbamates **6a–9a** as shown in Scheme 3. The reaction of **3** with alcohols proved trivial, with high purity being observed in every case. Mild acidification of aqueous solution of pyridinium salts **6–9** initially afforded target carbamates **6a–9a** in high yields (Scheme 3).

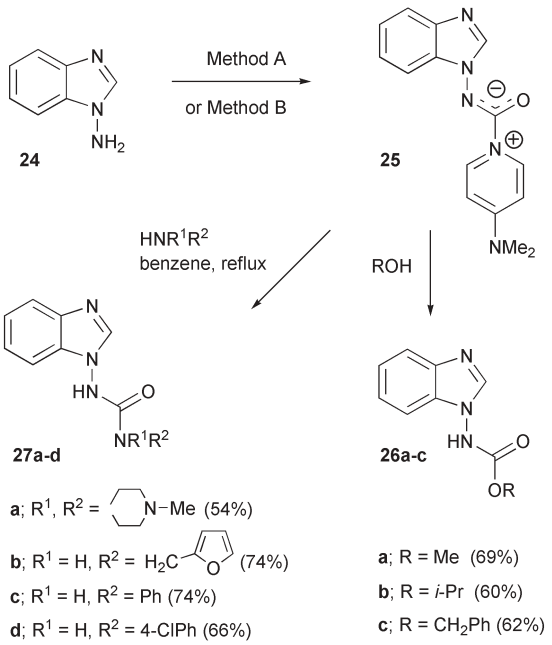
The success with benzenesulfonamides prompted us to try other substrate, namely 1-aminobenzimidazole (**24**). As anticipated, the reaction of **24** with the DPC/DMAP couple



Scheme 2 Preparation of 1,3-bis(arylsulfonyl)ureates **4a–c**.



Scheme 3 Preparation of *N*-(arylsulfonyl)carbamates **6a–9a** and arylsulfonylureas **10a–23a**.



Scheme 4 Preparation of 4-dimethylaminopyridinium *N*-(benzimidazol-1-yl)carbamoylide **25**, and corresponding carbamates **26a–c** and ureas **27a–d**. *Reagents, conditions and yields:* Method A: **24** (1.0 molar equiv.), DPC (1.1 molar equiv.), DMAP (1.1 molar equiv.), MeCN, reflux, 3 h, 67%; Method B: **24** (1.0 molar equiv.), CDI (1.1 molar equiv.), DMAP (1.1 molar equiv.), MeCN, reflux, 3 h, 83%.

provided carbamoylide **25** in 67% yield (Scheme 4, Method A). We further found that even better results could be obtained when *N*,*N*′-carbonyldiimidazole (CDI) was used in place of DPC (Scheme 4, Method B, yield 83% *vs.* 67%).

The identity of the newly synthesized carbamoylide **25** was proven by elemental analysis and spectroscopic data. When we compare the ^{1}H NMR spectra of compound **25** and the series **3**, there are no significant variations in the signals corresponding to the 4-dimethylaminopyridinium moiety, and the infrared spectrum of **25** exhibited a characteristic absorption band at 1710 cm^{-1} in close resemblance to those reported for carbamoylides **3a–e**.

Compound **25** readily combined with alcohols to give the corresponding carbamates **26a–c**. On the other hand, treatment of **25** with aliphatic and aromatic amines provided ureas **27a–d**. Both the carbamates **26** and ureas **27** were obtained in good yields.

Conclusion

The current work has addressed the use of environmentally non-hazardous arylsulfonamides and diphenyl carbonate in the synthesis of 4-dimethylaminopyridinium *N*-(arylsulfonyl)-carbamoylides, the stable and easy-to-handle substitutes of arylsulfonyl isocyanates. This is a significant improvement of the original procedures since problems associated with the use of isocyanates are avoided. Comparison of the existing literature methods for preparation of arylsulfonyl/heteroaryl carbamates and ureas from arylsulfonamides suggests that the DPC/DMAP approach is superior. Some of the advantages include mild reaction conditions, the ease of preparation and product separation and the extended shelf-life of the parent ylides. Moreover, a very high reactivity of pyridinium carbamoylides renders them suitable for the syntheses of arylsulfonyl(heteroaryl) urea- or carbamate-based combinatorial libraries.

Experimental

All solvents were dried by standard methods and experiments were carried out with exclusion of moisture. Melting points were determined on a Büchi SMP 20 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer using a mixture of the compound and KBr. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or Varian Unity Plus 500 spectrometer in DMSO-d$_6$, using Me$_4$Si as an internal standard. The coupling constants (*J*) are given in Hz. Mass spectra were recorded on a Finningan MAT 95 spectrometer at 70 eV. 1*H*-Benzimidazol-1-ylamine **24** was prepared according to the procedure described previously.[44] All other reagents and solvents were used as received from commercial suppliers.

General procedure for the synthesis of *N*-(arylsulfonyl)carbamoylides 3a–d

A solution of the corresponding sulfonamide **1a–d** (33 mmol), dimethylaminopyridine 8.06 g (66 mmol) and diphenyl carbonate 4.5 g (37 mmol) in acetonitrile (40 cm^3) was left to stand at room temperature for 18 h. Then, the resulting precipitate was filtered off, washed thoroughly with methanol (2 × 15 cm^3), and dried.

Yields, melting points, analytical and spectroscopic data of products 3a–d

4-Dimethylaminopyridinium *N*-(benzenesulfonyl)carbamoylide 3a. This compound was prepared from benzenesulfonamide **1a** (5.2 g); yield 5.8 g (58%); white solid (Found: C, 55.4; H, 4.7; N, 13.5. Calc. for $C_{14}H_{15}N_3O_3S$: C, 55.1; H, 4.9; N, 13.8%); mp 214–217 °C; ν_{max}(KBr)/cm^{-1} 1705, 1645, 1570, 1445, 1280, 1260, 1143 and 1075; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.27 (6 H, s, *CH*$_3$N*CH*$_3$), 6.99 (2 H, d, *J* 6.6, 3- and 5-H, pyrid.), 7.4–7.62 (3 H, m, Ph), 7.88–7.92 (2 H, m, Ph), 8.76 (2 H, d, *J* 6.6, 2- and 6-H, pyrid.).

4-Dimethylaminopyridinium *N*-(4-methylphenylsulfonyl)carbamoylide 3b. This compound was prepared from *p*-toluenesulfonamide **1b** (5.65 g); yield 6.8 g (65%); white solid (Found: C, 56.1; H, 5.7; N, 13.4. Calc. for $C_{15}H_{17}N_3O_3S$: C, 56.4; H, 5.4; N, 13.2%); mp 217–220 °C (lit.,[45] 220 °C); ν_{max}(KBr)/cm^{-1} 1710, 1650, 1570, 1445, 1280, 1255, 1145 and 1075; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 2.35 (3 H, s, CH$_3$), 3.25 (6 H, s, *CH*$_3$N*CH*$_3$), 6.98 (2 H, d, *J* 6.6, 3- and 5-H, pyrid.), 7.28 (2 H, d, *J* 7.0, 4-MePh), 7.76 (2 H, d, *J* 7.0, 4-MePh), 8.74 (2 H, d, *J* 6.6, 2- and 6-H, pyrid.).

4-Dimethylaminopyridinium *N*-(4-methoxyphenylsulfonyl)-carbamoylide 3c. This compound was prepared from 4-methoxybenzenesulfonamide **1c** (6.18 g); yield 6.88 g (62%); white solid (Found: C, 53.4; H, 5.3; N, 12.1. Calc. for $C_{15}H_{17}N_3O_4S$:

C, 53.7; H, 5.1; N, 12.5%); mp 214–216 °C; ν_{max}(KBr)/cm^{-1} 1705, 1645, 1590, 1570, 1495, 1280, 1245, 1140 and 1070; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.26 (6 H, s, *CH$_3$*N*CH$_3$*), 3.82 (3 H, s, OCH$_3$), 6.98 (2 H, d, *J* 6.7, 3- and 5-H, pyrid.), 7.02 (2 H, d, *J* 6.9, 4-MeOPh), 7.83 (2 H, d, *J* 6.9, 4-MeOPh), 8.75 (2 H, d, *J* 6.7, 2- and 6-H, pyrid.).

4-Dimethylaminopyridinium *N*-(4-chlorophenylsulfonyl)carbamoylide 3d. This compound was prepared from 4-chlorobenzenesulfonamide **1d** (6.32 g); 5.72 g (51%); white solid (Found: C, 49.3; H, 3.9; N, 12.5. Calc. for $C_{14}H_{14}ClN_3O_3S$: C, 49.5; H, 4.1; N, 12.4%); mp 221–223 °C; ν_{max}(KBr)/cm^{-1} 1705, 1645, 1295 and 1150; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.22 (6 H, s, *CH$_3$*N*CH$_3$*), 6.79 (2 H, d, *J* 7.8, 3- and 5-H, pyrid.), 7.54 (2 H, d, *J* 8.4, 4-ClPh), 7.86 (2 H, d, *J* 8.4, 4-ClPh), 8.71 (2 H, d, *J* 7.8, 2- and 6-H, pyrid.).

Separation of 4-dimethylaminopyridinium 4-chloro-*N*-(phenoxycarbonyl)benzenesulfonamidate 2d

A solution of 4-chlorobenzenesulfonamide **1d** (5.75 g, 30 mmol), diphenylcarbonate (7.71 g, 36 mmol) and 4-dimethylaminopyridine (4.9 g, 40 mmol) in acetonitrile (30 cm^3) was stirred vigorously at room temperature for 6 h. The resulting precipitate was filtered off, washed with acetonitrile (2 × 3 cm^3) and toluene (3 × 2 cm^3), and dried to give **2d** (5.6 g, 43%) as a white solid (Found: C, 55.7; H, 4.5; N, 9.9. Calc. for $C_{20}H_{20}ClN_3O_4S$: C, 55.4; H, 4.6; N, 9.7%); mp 162–163 °C; ν_{max}(KBr)/cm^{-1} 2900, 2770, 2665, 2500, 2030, 1685, 1645, 1290 and 1150; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.16 (6 H, s, *CH$_3$*N*CH$_3$*), 6.47 (2 H, d, *J* 7.3, 3- and 5-H, pyrid.), 6.89 (2 H, d, *J* 8.3, 4-ClPh), 7.05 (1 H, t, *J* 7.3, Ph), 7.25 (2 H, t, *J* 7.3, Ph), 7.46 (2 H, d, *J* 7.3, Ph), 7.76 (2 H, d, *J* 8.3, 4-ClPh), 8.2 (2 H, d, *J* 7.3, 2- and 5-H, pyrid.).

General procedure for the synthesis of 4-dimethylaminopyridinium 1,3-bis(arylsulfonyl)ureates 4a–c

A solution of the corresponding sulfonamide **1a–c** (33 mmol), 4-dimethylaminopyridine (4.5 g, 37 mmol) and diphenyl carbonate (7.5 g, 35 mmol) in acetonitrile (45 cm^3) was refluxed for 8 h. Then, after cooling to room temperature the precipitate of a mixture of **3** and **4** (NMR evidences) thus obtained was filtered off, dried and purified by fractional crystallization from DMF. The product **3** that precipitated upon cooling the DMF solution to 30 °C was separated by suction. The filtrate was then cooled to 15 °C and the product **4** thus obtained was collected by filtration.

Yields, melting points, analytical and spectroscopic data of products 4a–c

4-Dimethylaminopyridinium 1,3-bis(benzenesulfonyl)ureate 4a. This compound was prepared from benzenesulfonamide **1a** (5.2 g); yield 2.6 g (34%); white powder (Found: C, 52.3; H, 5.1; N, 12.4. Calc. for $C_{20}H_{22}N_4O_5S_2$: C, 52.0; H, 4.8; N, 12.1%); mp 179–183 °C; ν_{max}(KBr)/cm^{-1} 3150, 3090, 2920, 2815, 2695, 1665, 1640, 1560, 1445, 1420, 1260, 1245, 1160 and 1040; δ_H(500 MHz; DMSO-d$_6$; Me$_4$Si) 3.17 (6 H, s, *CH$_3$*N*CH$_3$*), 6.96 (2 H, d, *J* 7.8, 3- and 5-H, pyrid.), 7.42 (4 H, t, *J* 7.3, Ph), 7.47 (2 H, t, *J* 7.3, Ph), 7.7 (4 H, d, *J* 7.3, Ph), 8.2 (2 H, d, *J* 7.3, 2- and 6-H, pyrid.), 11.4 (1 H, br s, NH); δ_C(125 MHz; DMSO-d$_6$; Me$_4$Si) 39.5, 106.93, 126.8, 128.03, 130.94, 139.3, 143.71, 154.65, 156.87.

4-Dimethylaminopyridinium 1,3-bis(4-methylphenylsulfonyl)-ureate 4b. This compound was prepared from *p*-toluenesulfonamide **1b** (5.65 g); yield 3.4 g (42%); white powder (Found: C, 53.9; H, 5.5; N, 11.2. Calc. for $C_{22}H_{26}N_4O_5S_2$: C, 53.8; H, 5.3; N, 11.4%); mp 171–174 °C; ν_{max}(KBr)/cm^{-1} 3150, 3090, 2920, 2690, 1670, 1640, 1610, 1560, 1420, 1260, 1245, 1160, 1140 and 1040; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 2.36 (6 H, s, 2 × CH$_3$), 3.2 (6 H, s, *CH$_3$*N*CH$_3$*), 6.99 (2 H, d, *J* 6.9, 3- and 5-H, pyrid.), 7.24 (4 H, d, *J* 7.8, 4-MePh), 7.62 (4 H, d, *J* 7.7, 4-MePh), 8.21 (2 H, d, *J* 6.6, 2- and 6-H, pyrid.), 11.5 (1 H, br s, NH); δ_C(50 MHz; DMSO-d$_6$; Me$_4$Si) 21.2, 39.4, 107.21, 127.18, 128.74, 139.56, 141.13, 141.23, 154.89, 157.16.

4-Dimethylaminopyridinium 1,3-bis(4-methoxyphenyl-sulfonyl)ureate 4c. This compound was prepared from 4-methoxybenzenesulfonamide **1c** (6.18 g); yield 3.4 g (40%); white powder (Found: C, 50.3; H, 5.2; N, 10.4. Calc. for $C_{22}H_{26}N_4O_7S_2$: C, 50.6; H, 5.0; N, 10.7%); mp 159–161 °C; ν_{max}(KBr)/cm^{-1} 3170, 3100, 2925, 2690, 1665, 1640, 1600, 1560, 1500, 1415, 1255, 1240, 1155, 1130 and 1040; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.19 (6 H, s, *CH$_3$*N*CH$_3$*), 3.81 (6 H, s, 2 × OCH$_3$), 6.94–7.0 (6 H, m, 3- and 5-H, pyrid., and 4-MeOPh), 7.68 (4 H, d, *J* 8.9, 4-MeOPh), 8.21 (2 H, d, *J* 6.5, 2- and 6-H, pyrid.), 11.41 (1 H, br s, NH); δ_C(50 MHz; DMSO-d$_6$; Me$_4$Si) 39.4, 55.68, 107.22, 113.43, 129.18, 136.02, 139.64, 154.86, 156.1, 161.4.

Preparation of 1,3-bis(benzenesulfonyl)urea 5a

A mixture of **4a** (1 g, 2.5 mmol) in 1% hydrochloric acid (20 cm^3) was stirred at room temperature for 2 h. Then, the solid was collected by filtration, washed with water (3 × 2 cm^3), dried and crystallized from ethanol/water to give **5a** (0.44 g, 60%) as a white crystals (Found: C, 45.7; H, 3.6; N, 8.3. Calc. for $C_{13}H_{12}N_2O_5S_2$: C, 45.9; H, 3.5; N, 8.2%); mp 157–159 °C (lit.,[46] 153–154 °C); ν_{max}(KBr)/cm^{-1} 3335, 1745, 1445, 1345, 1190, 1170, 1135 and 1080; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 7.65–7.75 (6 H, m, Ph), 7.89–7.93 (4 H, m, Ph).

General procedure for the preparation of 4-dimethylaminopyridinium benzenesulfonamidates 6–9

A suspension of the appropriate 4-dimethylaminopyridinium *N*-(arylsulfonyl)carbamoylide **3a–b, d** (3.5 mmol) was refluxed for 1 min in anhydrous alcohol (6 cm^3) and then the solution obtained left to stand at room temperature overnight (in the case of **6**, **7**) or for 1 h (in the case of **8**, **9**). The resulting precipitate was filtered off, washed with alcohol (2 × 1 cm^3) and dried.

Yields, melting points, analytical and spectroscopic data of products 6–9

4-Dimethylaminopyridinium *N*-(methoxycarbonyl)benzenesulfonamidate 6. This compound was prepared from **3a** (1.07 g)

and methanol; yield 0.93 g (79%); white crystals (Found: C, 53.6; H, 5.4; N, 12.2. Calc. for $C_{15}H_{19}N_3O_4S$: C, 53.4; H, 5.7; N, 12.4%); mp 173–176 °C dec.; ν_{max}(KBr)/cm^{-1} 3115, 3080, 2945, 2055, 1950, 1670, 1635, 1550, 1420, 1295, 1250, 1145 and 1075; δ_H(500 MHz; DMSO-d$_6$; Me$_4$Si) 3.14 (6 H, s, *CH$_3$*N*CH$_3$*), 3.31 (3 H, s, OCH$_3$), 6.92 (2 H, d, *J* 6.7, 3- and 5-H, pyrid.), 7.41–7.47 (3 H, m, Ph), 7.74–7.75 (2 H, m, Ph), 8.19 (2 H, d, *J* 6.8, 2- and 6-H, pyrid.).

4-Dimethylaminopyridinium 4-methyl-*N*-(methoxycarbonyl)-benzenesulfonamidate 7. This compound was prepared from **3b** (1.12 g) and methanol; yield 1 g (80%); white crystals (Found: C, 54.5; H, 5.9; N, 12.3. Calc. for $C_{16}H_{21}N_3O_4S$: C, 54.7; H, 6.0; N, 12.0%); mp 147–150 °C dec.; ν_{max}(KBr)/cm^{-1} 3105, 3070, 2945, 2055, 1950, 1685, 1640, 1555, 1430, 1260, 1250, 1135 and 1075; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 2.33 (3 H, s, CH$_3$), 3.13 (6 H, s, *CH$_3$*N*CH$_3$*), 3.32 (3 H, s, OCH$_3$), 6.9 (2 H, d, *J* 6.0, 3- and 5-H, pyrid.), 7.22 (2 H, d, *J* 8.3, 4-MePh), 7.64 (2 H, d, *J* 8.2, 4-MePh), 8.19 (2 H, d, *J* 6.0, 2- and 6-H, pyrid.).

4-Dimethylaminopyridinium 4-methyl-*N*-(ethoxycarbonyl)-benzenesulfonamidate 8. This compound was prepared from **3b** (1.12 g) and ethanol; yield 1 g (78%); white powder (Found: C, 55.6; H, 6.0; N, 11.3. Calc. for $C_{17}H_{23}N_3O_4S$: C, 55.9; H, 6.3; N, 11.5%); mp 150–151 °C dec.; ν_{max}(KBr)/cm^{-1} 3105, 3065, 2075, 1970, 1645, 1555, 1275, 1135, 1100 and 1070; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 1.03 (3 H, t, *J* 7.1, CH$_2$*CH$_3$*), 2.33 (3 H, s, CH$_3$), 3.12 (6 H, s, *CH$_3$*N*CH$_3$*), 3.77 (2 H, q, *J* 7.1, *CH$_2$*CH$_3$), 6.9 (2 H, d, *J* 6.4, 3- and 5-H, pyrid.), 7.23 (2 H, d, *J* 7.7, 4-MePh), 7.65 (2 H, d, *J* 7.7, 4-MePh), 8.18 (2 H, d, *J* 6.2, 2- and 6-H, pyrid.).

4-Dimethylaminopyridinium 4-chloro-*N*-(methoxycarbonyl)-benzenesulfonamidate 9. This compound was prepared from **3d** (1.2 g) and methanol; yield 1.1 g (84%); white crystals (Found: C, 48.5; H, 4.6; N, 11.4. Calc. for $C_{15}H_{18}ClN_3O_4S$: C, 48.4; H, 4.9; N, 11.3%); mp 169–170 °C dec.; ν_{max}(KBr)/cm^{-1} 2750, 2635, 2515, 2250, 2030, 1675, 1645, 1295 and 1150; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.19 (6 H, s, *CH$_3$*N*CH$_3$*), 3.33 (3 H, s, OCH$_3$), 7.0 (2 H, d, *J* 6.2, 3- and 5-H, pyrid.), 7.49 (2 H, d, *J* 7.7, 4-ClPh), 7.77 (2 H, d, *J* 7.7, 4-ClPh), 8.24 (2 H, d, *J* 6.2, 2- and 6-H, pyrid.).

Preparation of *N*-(arylsulfonyl)carbamates 6a–9a

To a suspension of the corresponding sulfonamidate **6–9** (2.5 mmol) in water (20 cm^3), 10% hydrochloric acid (10 cm^3) was added with stirring, and then stirred at room temperature for 0.5 h. The precipitate was filtered off, washed with water (2 × 0.5 cm^3), and dried initially at room temperature and then at 60 °C.

Yields, melting points, analytical and spectroscopic data of products 6a–9a

Methyl *N*-benzenesulfonylcarbamate 6a. This compound was prepared from **6** (0.84 g); yield 1.3 g (87%); mp 130–132 °C (lit.,[47a] 131–131.8 °C).

Methyl *N*-(4-methylphenylsulfonyl)carbamate 7a. This compound was prepared from **7** (0.88 g); yield 0.51 g (90%); mp 106–107 °C (lit.,[47b] 107–109 °C).

Ethyl *N*-(4-methylphenylsulfonyl)carbamate 8a. This compound was prepared from **8** (0.91 g); yield 0.47 g (78%); mp 79–81 °C (lit.,[47c] 80–82 °C).

Methyl *N*-(4-chlorophenylsulfonyl)carbamate 9a. This compound was prepared from **9** (0.93 g); yield 0.53 g (84%); mp 129–130 °C (lit.,[47b] 132 °C).

General procedure for the preparation of arylsulfonylureates 10–23

To a stirred solution of the appropriate amine (6 mmol or 10 mmol in the case of butylamine and propylamine) in acetonitrile (15 cm^3) *N*-(arylsulfonyl)carbamoylide **3a–d** (5 mmol) was added, and then refluxed for 5 or 30 min (in the case of aniline). After cooling to room temperature, the precipitate thus obtained was filtered off, washed with acetonitrile and methanol (2 × 0.5 cm^3), and dried.

Yields, melting points, analytical and spectroscopic data for selected products 13, 14, 17, 21, 22, 23

4-Dimethylaminopyridinium 1-benzenesulfonyl-3-(phenyl)-1-ureate 13. This compound was prepared from **3a** (1.83 g) and aniline (0.56 g, 0.54 cm^3); yield 1.6 g (65%); beige crystals (Found: C, 60.1; H, 5.3; N, 14.3. Calc. for $C_{20}H_{22}N_4O_3S$: C, 60.3; H, 5.6; N, 14.1%); mp 155–158 °C; ν_{max}(KBr)/cm^{-1} 3312, 3055, 2925, 2675, 1650, 1630, 1565, 1525, 1435, 1315, 1255, 1235, 1210 and 1140; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 3.15 (6 H, s, *CH$_3$*N*CH$_3$*), 6.76–6.83 (1 H, m, Ph), 6.92 (2 H, d, *J* 6.1, 3- and 5-H pyrid.), 7.09–7.17 (2 H, m, Ph), 7.41–7.47 (5 H, m, Ph), 7.81–7.87 (2 H, m, Ph), 8.21 (2 H, d, *J* 6.1, 2- and 6-H, pyrid.), 8.51 (1 H, s, Ph*NH*).

Butylaminium 3-butyl-1-(4-methylphenylsulfonyl)-1-ureate 14. This compound was prepared from **3b** (1.6 g) and butylamine (0.73 g, 0.99 cm^3); 1.4 g (84%); white powder (Found: C, 55.6; H, 8.7; N, 12.4. Calc. for $C_{16}H_{29}N_3O_3S$: C, 55.9; H, 8.5; N, 12.2%); mp 117–120 °C; ν_{max}(KBr)/cm^{-1} 3335, 3080, 2959, 2875, 2660, 2545, 1685, 1600, 1530, 1245, 1125 and 1085; δ_H(200 MHz; DMSO-d$_6$; Me$_4$Si) 0.77–0.88 (6 H, m, 2 × CH$_2$*CH$_3$*), 1.12–1.52 (8 H, m, 2 × CH$_2$CH$_2$), 2.3 (3 H, s, CH$_3$), 2.68–2.86 (4 H, m, 2 × NH*CH$_2$*), 6.02 (1H, br s, *NH*CH$_2$), 7.16 (2 H, d, *J* 8.1, 4-MePh), 7.34 (3 H, br s, H$_3$N$^+$), 7.6 (2 H, d, *J* 8.2, 4-MePh).

4-Dimethylaminopyridinium-1-(4-methylphenylsulfonyl)-3-(thiophen-2-ylmethyl)-1-ureate 17. This compound was prepared from **3b** (1.6 g) and 2-(aminomethyl)thiophen (0.68 g, 0.62 cm^3); yield 2 g (93%); white powder (Found: C, 55.4; H, 5.7; N, 13.2. Calc. for $C_{20}H_{24}N_4O_3S_2$: C, 55.1; H, 5.5; N, 12.9%); mp 173–175 °C; ν_{max}(KBr)/cm^{-1} 3205, 3160, 3025, 2915, 1645, 1600, 1550, 1300, 1255, 1210, 1125 and 1075; δ_H(500 MHz; DMSO-d$_6$; Me$_4$Si) 2.36 (3 H, s, CH$_3$), 3.02 (6 H, s, *CH$_3$*N*CH$_3$*), 4.29 (2 H, d, *J* 4.9, CH$_2$), 6.7 (2 H, d, *J* 6.3, 3- and 5-H, pyrid.), 6.81–6.82 (1 H, m, CH), 6.9 (1 H, t, *J* 3.9,

CH), 6.95 (1 H, br s, NH), 7.3–7.34 (3 H, m, 4-MePh and CH), 7.72 (2 H, d, *J* 7.3, 4-MePh), 8.13 (2 H, d, *J* 6.3, 2- and 6-H, pyrid.).

Propylaminium 1-(4-chlorophenylsulfonyl)-3-(propyl)-1-ureate 21. This compound was prepared from **3d** (1.7 g) and propylamine (0.59 g, 0.82 cm^3); yield 1.3 g (80%); white powder (Found: C, 46.5; H, 5.9; N, 12.6. Calc. for $C_{13}H_{22}ClN_3O_3S$: C, 46.8; H, 6.0; N, 12.6%); mp 133–134 °C; ν_{max}(KBr)/cm^{-1} 3335, 2785, 2720, 2645, 2545, 2060, 1685, 1305 and 1130; δ_H(200 MHz; DMSO-d_6; Me_4Si) 0.75 (3 H, t, *J* 7.3, CH_3), 0.81 (3 H, t, *J* 7.5, CH_3), 1.28 (2 H, sext., *J* 7.3, CH_2), 1.52 (2 H, sext., *J* 7.5, CH_2), 2.67–2.82 (4 H, m, 2 × NCH_2), 7.40 (2 H, d, *J* 8.5, 4-ClPh), 7.69 (3 H, br s, H_3N^+), 7.71 (2 H, d, *J* 8.5, 4-ClPh).

4-Dimethylaminopyridinium 1-(4-chlorophenylsulfonyl)-3-(furfuryl)-1-ureate 22. This compound was prepared from **3d** (1.7 g) and furfurylamine (0.58 g, 0.53 cm^3); yield 2.0 g (91%); white powder (Found: C, 51.9; H, 4.7; N, 12.8. Calc. for $C_{19}H_{21}ClN_4O_4S$: C, 52.2; H, 4.8; N, 12.8%); mp 156–157 °C; ν_{max}(KBr)/cm^{-1} 3225, 2900, 2780, 2690, 2510, 2060, 1645, 1295 and 1130; δ_H(200 MHz; DMSO-d_6; Me_4Si) 3.12 (6 H, s, CH_3NCH_3), 4.13 (2 H, d, *J* 4.9, CH_2), 6.12 (1 H, d, *J* 2.3, CH), 6.36 (1 H, m, CH), 6.63 (1H, br s, NH), 6.85 (2 H, d, *J* 5.8, 3- and 5-H, pyrid.), 7.51–7.55 (3 H, m, 4-ClPh and CH), 7.81 (2 H, d, *J* 8.3, 4-ClPh), 8.19 (2 H, d, *J* 5.8, 2- and 6-H pyrid.).

4-Dimethylaminopyridinium 1-(4-chlorophenylsulfonyl)-3-(phenyl)-1-ureate 23. This compound was prepared from **3d** (1.7 g) and aniline (0.56 g, 0.54 cm^3); yield 2.1 g (97%); white powder (Found: C, 55.2; H, 5.2; N, 13.1. Calc. for $C_{20}H_{21}ClN_4O_3S$: C, 55.5; H, 4.9; N, 12.9%); mp 166–167 °C; ν_{max}(KBr)/cm^{-1} 3315, 2910, 2780, 2680, 2500, 2250, 1650, 1630, 1310 and 1140; δ_H(200 MHz; DMSO-d_6; Me_4Si) 3.14 (6 H, s, CH_3NCH_3), 6.75 (1 H, t, *J* 7.8, Ph), 6.93 (2 H, d, *J* 7.0, 3- and 5-H, pyrid.), 7.09 (2 H, t, *J* 7.8, Ph), 7.13 (2H, t, *J* 7.8, Ph), 7.46 (2 H, d, *J* 8.4, 4-ClPh), 7.81 (2 H, d, *J* 8.4, 4-ClPh), 8.2 (2 H, d, *J* 7.0, 2- and 6-H, pyrid.), 8.49 (1 H, s, Ph*NH*).

Preparation of arylsulfonylureas 10a–23a

A suspension of the corresponding ureate **10–23** (3 mmol) in water (10 cm^3) was acidified with 1% hydrochloric acid to pH 2.3–2.5 or 4–4.3 (in the case of 2-picoline), and then stirred at room temperature for 1 h. The precipitate thus obtained was filtered off, washed thoroughly with water and methanol (3 × 0.5 cm^3), and dried initially at room temperature and then at 60 °C.

Yields, melting points, analytical and spectroscopic data of products 10a–23a

***N*-(Pyrrolidin-1-ylcarbonyl)benzenesulfonamide 10a.** This compound was prepared from **10** (1.09 g); yield 0.44 g (60%); white solid (Found: C, 51.2; H, 5.4; N, 11.3. Calc. for $C_{11}H_{14}N_2O_3S$: C, 51.9; H, 5.5; N, 11.0%); mp 204–206 °C (MeOH); ν_{max}(KBr)/cm^{-1} 3155, 2975, 2875, 1660, 1455, 1390, 1180, 1165 and 1070; δ_H(200 MHz; DMSO-d_6; Me_4Si) 1.75 (4 H, s, 2 × CH_2), 3.17 (4 H, s, CH_2NCH_2), 7.53–7.72 (3 H, m, Ph), 7.89–7.93 (2 H, m, Ph), 10.72 (1 H, s, SO_2NH); *m*/*z* (EI) 254.2 (M^+, <1%), 183 (10), 157 (13), 141 (28), 97 (17), 77 (100) and 71 (6).

1-Benzenesulfonyl-3-furfurylurea 11a. This compound was prepared from **11** (1.2 g); yield 0.82 g (98%); white solid (Found: C, 51.1; H, 4.6; N, 10.2. Calc. for $C_{12}H_{12}N_2O_4S$: C, 51.4; H, 4.3; N, 10.0%); mp 156–158 °C; ν_{max}(KBr)/cm^{-1} 3330, 3185, 3120, 2925, 1660, 1545, 1475, 1340 and 1155; δ_H(200 MHz; DMSO-d_6; Me_4Si) 4.14 (2 H, d, *J* 5.6, CH_2), 6.12 (1 H, d, *J* 3.0, CH), 6.34 (1 H, t, *J* 2.9, CH), 6.94 (1 H, t, *J* 5.6, NH), 7.53–7.71 (4 H, m, Ph and CH), 7.88–7.92 (2 H, m, Ph), 10.74 (1 H, br s, SO_2NH).

1-Benzenesulfonyl-3-(pyridin-2-ylmethyl)urea 12a. This compound was prepared from **12** (1.24 g); yield 0.84g (97%); white solid (Found: C, 53.4; H, 4.3; N, 14.2. Calc. for $C_{13}H_{13}N_3O_3S$: C, 53.6; H, 4.5; N, 14.4%); mp 142–144 °C; ν_{max}(KBr)/cm^{-1} 3365, 3335, 3185, 3125, 2920, 1665, 1550, 1475, 1335 and 1160; δ_H(200 MHz; DMSO-d_6; Me_4Si) 4.27 (2 H, d, *J* 2.8, CH_2), 7.11–7.2 (3 H, m, Ph and CH), 7.6–7.84 (4 H, m, Ph and NH), 7.9–7.93 (2 H, m, 2 × CH); 8.48 (1 H, s, CH), 10.9 (1 H, br s, SO_2NH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 44.72, 121.17, 122.48, 127.43 (two overlapping signals), 129.32 (two overlapping signals), 133.48, 136.98, 140.48, 149.05, 151.78, 157.81; *m*/*z* (EI) 291.2 (M^+, <1%), 184 (16), 141 (33) and 77 (100).

1-Benzenesulfonyl-3-phenylurea 13a. This compound was prepared from **13** (1.2 g); yield 0.67 g (80%); white powder (Found: C, 56.6; H, 4.1; N, 10.2. Calc. for $C_{13}H_{12}N_2O_3S$: C, 56.5; H, 4.4; N, 10.14%); mp 154–156 °C (lit.,[48a] 158–160 °C); ν_{max}(KBr)/cm^{-1} 3355, 3305, 3260, 1700, 1600, 1545, 1455, 1340 and 1165; δ_H(200 MHz; DMSO-d_6; Me_4Si) 7.04 (1 H, t, *J* 6.3, Ph), 7.24–7.38 (4 H, m, Ph), 7.62–7.77 (3 H, m, Ph), 8.0 (2 H, d, *J* 7.6, Ph), 8.89 (1 H, s, Ph*NH*), 10.82 (1 H, br s, SO_2NH).

1-Butyl-3-(4-methylphenylsulfonyl)urea 14a (*Tolbutamide*). This compound was prepared from **14** (1.03 g); yield 0.73 g (90%); mp 124–126 °C (lit.,[24] 126 °C).

3-Furfuryl-1-(4-methylphenylsulfonyl)urea 15a. This compound was prepared from **15** (1.25 g); yield 0.82 g (93%); white solid (Found: C, 53.3; H, 4.6; N, 9.2. Calc. for $C_{13}H_{14}N_2O_4S$: C, 53.0; H, 4.8; N, 9.5%); mp 167–169 °C; ν_{max}(KBr)/cm^{-1} 3325, 3166, 3120, 1660, 1540, 1340 and 1165; δ_H(500 MHz; DMSO-d_6; Me_4Si) 2.39 (3 H, s, CH_3), 4.15 (2 H, d, *J* 5.5, CH_2), 6.13 (1 H, s, CH), 6.35 (1 H, s, CH), 6.9 (1 H, t, *J* 5.6, NH), 7.4 (2 H, d, *J* 8.2, 4-MePh), 7.54 (1 H, s, CH), 7.78 (2 H, d, *J* 8.1, 4-MePh), 10.65 (1 H, br s, SO_2NH); δ_C(125 MHz; DMSO-d_6; Me_4Si) 21.74, 36.73, 107.56, 111.13, 127.98 (two overlapping signals), 130.14 (two overlapping signals), 138.02, 142.91, 144.37, 151.98, 152.66.

1-(4-Methylphenylsulfonyl)-3-(pyridin-2-ylmethyl)urea 16a. This compound was prepared from **16** (1.28 g); yield 0.85 g (93%); white solid (Found: C, 55.4; H, 4.7; N, 14.0. Calc. for $C_{14}H_{15}N_3O_3S$: C, 55.1; H, 4.9; N, 13.8%); mp 186–188 °C; ν_{max}(KBr)/cm^{-1} 3300, 1675, 1525, 1330, 1160, 1150 and 1090; δ_H(200 MHz; DMSO-d_6; Me_4Si) 2.38 (3 H, s, CH_3), 4.27

(2 H, d, *J* 5.5, CH_2), 7.13 (2 H, d, *J* 8.1, 2 × CH), 7.21–7.27 (1 H, m, NH), 7.39 (2 H, d, *J* 8.0, 4-MePh), 7.66–7.75 (1 H, m, CH), 7.79 (2 H, d, *J* 8.1, 4-MePh), 8.48 (1 H, d, *J* 4.5, CH), 10.81 (1 H, br s, SO_2NH).

1-(4-Methylphenylsulfonyl)-3-(thiophen-2-ylmethyl)urea 17a. This compound was prepared from **17** (1.3 g); yield 0.85 g (90%); white powder (Found: C, 50.1; H, 4.3; N, 9.2. Calc. for $C_{13}H_{14}N_2O_3S_2$: C, 50.3; H, 4.5; N, 9.0%); mp 178–181 °C; ν_{max}(KBr)/cm^{-1} 3320, 3160, 3100, 2885, 1660, 1540, 1320 and 1160; δ_H(200 MHz; DMSO-d_6; Me_4Si) 2.4 (3 H, s, CH_3), 4.32 (2 H, d, *J* 5.9, CH_2), 6.89–6.92 (2 H, m, 2 × CH), 7.05 (1 H, t, *J* 5.5, NH), 7.36–7.42 (3 H, m, 4-MePh and CH), 7.79 (2 H, d, *J* 8.1, 4-MePh), 10.74 (1 H, br s, SO_2NH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 21.31, 38.13, 125.38, 125.72, 126.91, 127.49 (two overlapping signals), 129.69 (two overlapping signals), 137.66, 142.38, 143.88, 151.62.

1-(4-Methylphenylsulfonyl)-3-phenylurea 18a. This compound was prepared from **18** (1.24 g); yield 0.78 g (90%); mp 169–171 °C (lit.,[48a] 170–172 °C).

3-Furfuryl-1-(4-methoxyphenylsulfonyl)urea 19a. This compound was prepared from **19** (1.29 g); yield 0.86 g (93%); white powder (Found: C, 50.6; H, 4.1; N, 9.2. Calc. for $C_{13}H_{14}N_2O_5S$: C, 50.3; H, 4.5; N, 9.0%); mp 162–163 °C; ν_{max}(KBr)/cm^{-1} 3315, 3110, 2905, 1655, 1595, 1545, 1340, 1265 and 1165; δ_H(200 MHz; DMSO-d_6; Me_4Si) 3.86 (3 H, s, OCH_3), 4.17 (2 H, d, *J* 5.8, CH_2), 6.16 (1 H, d, *J* 3.0, CH), 6.36–6.38 (1 H, m, CH), 6.9 (1 H, t, *J* 5.5, NH), 7.13 (2 H, d, *J* 8.0, 4-MeOPh), 7.81 (2 H, d, *J* 8.1, 4-MeOPh), 10.58 (1 H, br s, SO_2NH).

1-(4-Methoxyphenylsulfonyl)-3-phenylurea 20a. This compound was prepared from **20** (1.25 g); yield 0.84 g (92%); mp 148–149 °C (lit.,[48b] 150 °C).

1-(4-Chlorophenylsulfonyl)-3-propylurea 21a (*Chlorpropamide*). This compound was prepared from **21** (1.0 g); yield 0.8 g (94%); white powder; mp 129–130 °C (lit.,[24] 128 °C).

1-(4-Chlorophenylsulfonyl)-3-furfurylurea 22a. This compound was prepared from **22** (1.31 g); yield 0.9 g (95%); mp 169–170 °C (lit.,[48c] 170–171 °C).

1-(4-Chlorophenylsulfonyl)-3-phenylurea 23a. This compound was prepared from **23** (1.3 g), yield 0.85 g (91%); mp 172–173 °C (lit.,[48d] 179–181 °C).

Preparation of 4-dimethylaminopyridinium *N*-(benzimidazol-1-yl)carbamoylide 25

Method A. To a suspension of 1*H*-benzimidazol-1-ylamine **24** (1.33 g, 10 mmol) and diphenyl carbonate (DPC, 2.36 g, 11 mmol) DMAP (1.34 g, 11 mmol) was added and then refluxed for 3 h. The resulting mixture, after cooling to room temperature, was filtered off, washed with acetonitrile (3 × 2 cm^3) and dried to give **25** (1.87 g, 67%) as a yellow powder (Found: C, 64.4; H, 5.4; N, 25.1. Calc. for $C_{15}H_{15}N_5O$: C, 64.0; H, 5.4; N, 24.9%); mp 223–226 °C, decomp.; ν_{max}(KBr)/cm^{-1}: 3145, 2925, 1710, 1640, 1565, 1445, 1270, 1210, 1120, 1105 and 1065; δ_H (200 MHz; DMSO-d_6; Me_4Si) 3.3 (6 H, s, CH_3NCH_3), 7.08 (2 H, d, *J* 7.41, 3- and 5-H, pyrid.), 7.5–7.7 (3 H, m, 3 × CH), 7.75 (1 H, d, *J* 7.0, CH), 8.4 (1 H, s, 2-H, benzimidazole), 9.09 (2 H, d, *J* 7.3, 2- and 6-H, pyrid.).

Method B. To a solution of **24** (1.33 g, 10 mmol) and *N*,*N*′-carbonyldiimidazole (CDI, 1.78 g. 11 mmol) in acetonitrile (15 cm^3) DMAP (1.34 g, 11 mmol) was added, and then the reaction was carried out according to the procedure described above for the method A to give **25** (2.22 g, 83%), which was identical with the product obtained in method A.

The above described pyridinium carbamoylide **25** was used in the next step without further purification.

Preparation of carbamates 26a–b

A mixture of **25** (0.5 g, 1.8 mmol) in appropriate anhydrous alcohol (15 cm^3) was refluxed for 2 h. Then, the resulting solution was evaporated under reduced pressure and the solid residue was treated with water (20 cm^3). The insoluble product thus obtained was collected by filtration, washed with water (3 × 2 cm^3) and dried.

Yields, melting points, analytical and spectroscopic data of products 26a–b

Methyl benzimidazol-1-ylcarbamate 26a. This compound was prepared from methanol; yield 0.24 g (69%), white solid (Found: C, 56.4; H, 4.4; N, 21.9. Calc. for $C_9H_9N_3O_2$: C, 56.5; H, 4.7; N, 22.0%); mp 199–201 °C; ν_{max}(KBr)/cm^{-1}: 3100, 2950, 2920, 2850, 2745, 1740, 1550, 1275, 1225 and 1050; δ_H(200 MHz; DMSO-d_6; Me_4Si) 3.78 (3 H, s, OCH_3), 7.23–7.44 (3 H, m, 3 × CH), 7.73–7.76 (m, 1H, CH), 8.38 (1 H, s, 2-H, benzimidazole), 11.02 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 53.22, 109.52, 120.23, 122.6, 123.71, 133.7, 141.21, 144.67, 156.17.

Isopropyl benzimidazol-1-ylcarbamate 26b. This compound was prepared from isopropanol; yield 0.36 g (60%); white solid (Found: C, 60.6; H, 6.2; N, 19.5. Calc. for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 6.0; N, 19.2%); mp 143–145 °C; ν_{max}(KBr)/cm^{-1} 3135, 3095, 2985, 2930, 2875, 2775, 1745, 1730 1540, 1260, 1225 and 1105; δ_H(500 MHz; DMSO-d_6; Me_4Si) 1.29 (6 H, br s, 2 × CH_3), 4.9–4.92 (1 H, m, OCH), 7.25–7.28 (1 H, m, CH), 7.3–7.33 (1 H, m, CH), 7.35–7.37 (1 H, m, CH), 7.69 (1 H, d, *J* 8.3, CH), 8.32 (1 H, s, 2-H, benzimidazole), 10.92 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 22.06 (two overlapping signals), 69.89, 109.45, 120.23, 122.54, 123.67, 133.74, 141.23, 144.73, 155.27; *m*/*z* (EI) 219.2 (M^+, 63%), 160 (13), 133 (62) and 43 (100).

Preparation of benzyl benzimidazol-1-ylcarbamate 26c

A mixture of **25** (0.5 g, 1.8 mmol) and benzyl alcohol (0.24 g, 0.23 cm^3, 2.2 mmol) in benzene (15 cm^3) was refluxed for 2 h. Then, the resulting solution was evaporated under reduce pressure and the solid residue was treated with water (20 cm^3).

The insoluble product thus obtained was collected by filtration, washed with water (3 × 2 cm^3), dried and crystallized from ethyl acetate to give **26c** (0.31 g, 62%) as a white powder (Found: C, 67.0; H, 4.6; N, 15.4. Calc. for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.7%); mp 147–149 °C; ν_{max}(KBr)/cm^{-1} 3160, 2965, 1745, 1525, 1495, 1245, 1225 and 1035; δ_H(200 MHz; DMSO-d_6; Me_4Si) 5.26 (2 H, s, OCH_2), 7.23–7.67 (8 H, m, Ph and CH), 7.75 (1 H, d, *J* 7.0, CH), 8.42 (1H, s, 2-H, benzimidazole), 11.21 (1 H, br s, NH); δ_C (50 MHz; DMSO-d_6; Me_4Si) 67.4, 109.51, 120.26, 122.66, 123.76, 128.34, 128.57, 128.81 (two overlapping signals), 133.7, 136.17, 141.19, 144.71, 155.63.

Preparation of *N*-(benzimidazol-1-yl)-4-methylpiperazine-1-carboxamide 27a

A mixture of **25** (0.5 g, 1.8 mmol) and 4-methylpiperazine (0.2 g, 0.22 cm^3, 2 mmol) in anhydrous benzene (15 cm^3) was refluxed for 2 h. After cooling to room temperature, the precipitate was filtered off, washed with benzene (3 × 2 cm^3) and purified by crystallization from ethyl acetate to afford **27a** (0.26 g, 54%) as a white powder (Found: C, 60.45; H, 6.9; N, 27.0. Calc. for $C_{13}H_{17}N_5O$: C, 60.2; H, 6.6; N, 27.0%); mp 195–197 °C; ν_{max}(KBr)/cm^{-1} 3220, 3120, 3055, 2935, 2790, 1655, 1540, 1265, 1230 and 1145; δ_H(200 MHz; DMSO-d_6; Me_4Si) 2.27 (3 H, s, CH_3), 2.35–2.45 (4 H, m, 2 × CH_2), 3.44–3.57 (4 H, m, 2 × CH_2), 7.27–7.36 (3 H, m, 3 × CH), 7.71 (1 H, d, *J* 7.7, CH), 8.25 (1 H, s, 2-H, benzimidazole), 10.31 (1 H, br s, CONH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 43.78 (two overlapping signals), 46.04, 54.53 (two overlapping signals), 109.84, 120.03, 122.15, 123.2, 134.38, 141.33, 145.31, 155.86.

General procedure for the synthesis of ureas 27b–d

A mixture of **25** (0.5 g, 1.8 mmol) and the appropriate amine (2 mmol) in anhydrous benzene (15 cm^3) was refluxed for 2 h. After cooling to room temperature, the precipitate was filtered off, washed with water (20 cm^3) and dried.

Yields, melting points, analytical and spectroscopic data of products 27b–d

1-(Benzimidazol-1-yl)-3-furfurylurea 27b. This compound was prepared from furfurylamine (0.19 g, 0.18 cm^3, 2 mmol); yield 0.35 g (74%); white solid (Found: C, 60.7; H, 4.65; N, 22.0. Calc. for $C_{13}H_{12}N_4O_2$: C, 60.9; H, 4.7; N, 21.9%); mp 206–208 °C; ν_{max}(KBr)/cm^{-1} 3190, 3095, 2920, 1680, 1550, 1320 and 1235; δ_H(200 MHz; DMSO-d_6; Me_4Si) 4.3 (2 H, d, *J* 5.5, CH_2), 6.28 (1 H, d, *J* 2.85, CH, furane), 6.44 (1 H, s, CH, furane), 7.25–7.35 (3 H, m, 3 × CH), 7.49 (1 H, t, *J* 5.6, NH), 7.63 (1 H, s, CH, furane), 7.72 (1 H, d, *J* 7.0, CH), 8.26 (1 H, s, 2-H, benzimidazole), 9.73 (1 H, s, CONH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 36.8, 106.85, 109.71, 110.75, 120.08, 122.25, 123.31, 134.35, 141.44, 142.28, 145.38, 153.08, 156.81.

1-(Benzimidazol-1-yl)-3-phenylurea 27c. This compound was prepared from aniline (0.19 g, 0.19 cm^3, 2 mmol); yield 0.35 g (74%); white solid (Found: C, 66.4; H, 4.6; N, 22.2. Calc. for $C_{14}H_{12}N_4O$: C, 66.7; H, 4.8; N, 22.2%); mp 209–210 °C; ν_{max}(KBr)/cm^{-1} 3420, 3185, 2850, 2740, 1715, 1675, 1600, 1535, 1440, 1315 and 1210; δ_H(200 MHz; DMSO-d_6; Me_4Si) 7.0–7.08 (1 H, m, Ph), 7.25–7.55 (7 H, m, Ph and CH), 7.72–7.76 (1 H, m, CH), 8.34 (1 H, s, 2-H, benzimidazole), 9.54 (1 H, s, Ph*NH*), 9.87 (1 H, s, CONH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 109.82, 119.15, 120.09, 122.3, 122.8, 123.4, 128.61, 129.04 (two overlapping signals), 134.42, 139.45, 141.38, 145.46, 154.5.

1-(Benzimidazol-1-yl)-3-(4-chlorophenyl)urea 27d. This compound was prepared from *p*-chloroaniline (0.25 g, 2 mmol); yield 0.35 g (66%), white powder (Found: C, 58.3; H, 4.0; N, 19.6. Calc. for $C_{14}H_{11}ClN_4O$: C, 58.6; H, 3.9; N, 19.5%); mp 232–233 °C (*i*-PrOH); ν_{max}(KBr)/cm^{-1} 3270, 3190, 3125, 1685, 1600, 1545, 1490, 1400, 1310, 1245 and 1215; δ_H(200 MHz; DMSO-d_6; Me_4Si) 7.29–7.47 (5 H, m, 4-ClPh and 3 × CH), 7.55–7.59 (2 H, m, 4-ClPh), 7.74 (1 H, d, *J* 7.0, CH), 8.35 (1 H, s, 2-H, benzimidazole), 9.71 (1 H, s, 4-ClPh*NH*), 9.97 (1 H, s, CONH); δ_C(50 MHz; DMSO-d_6; Me_4Si) 109.82, 120.1, 120.69 (two overlapping signals), 122.33, 123.43, 126.4, 128.91 (two overlapping signals), 134.37, 138.49, 141.36, 145.4, 154.44.

References

1 J. M. Goldman, *Drugs Today*, 1989, **321**, 1231.
2 H. Akita, K. Kurashima, M. Nozawa, S. Yamamura, K. Seri and Y. Imamura, *Tetrahedron: Assym.*, 1998, **9**, 4331.
3 R. Perfetti and A. Ahmad, *Trends Endocrin. Met.*, 2000, **11**, 218.
4 H. A. Friedel and M. T. T. Buckley, *Drugs*, 1991, **41**, 81.
5 G. Levitt, in *Pesticide Chemistry: Human Walfare and Environment*, ed. J. Miymato and P. C. Kearney, Pergamon, New York, 1983, vol. 1, p. 243.
6 B. M. Berger and N. L. Wolfe, *Environ. Toxicol. Chem.*, 1996, **15**, 1500.
7 R. Galeazzi, C. Murucchini, M. Orena and C. Zodra, *Bioorg. Med. Chem.*, 2002, **10**, 1019.
8 T. R. Ren, H. W. Yang, X. Gao, X. L. Yang, J. J. Zhan and F. H. Cheng, *Pest Manag. Sci.*, 2000, **56**, 218.
9 J. E. Toth, G. B. Grindey, W. J. Ehlhardt, J. E. Ray, G. B. Boder, J. R. Bewley, K. G. Klingerman, S. B. Gates, S. M. Rinzel, R. M. Schultz, L. C. Weir and J. F. Worzalla, *J. Med. Chem.*, 1997, **40**, 1018.
10 M. J. Gil, M. A. Manu, C. Artaega, M. Migliaccio, I. Enfco and G. A. Martinez-Merino, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2321.
11 J. J. Howbert, *Drug Future*, 1991, **16**, 517.
12 G. B. Boder, W. J. Ehlhardt, G. B. Grindley, P. J. Houghton, D. L. Kau, F. Mohamadi, D. E. Seltz, W. N. Shaw and J. E. Toth, *Drug Future*, 1992, **17**, 1111.
13 P. Lehr, A. Billich, B. Wolff and P. Nussbaumer, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1235.
14 P. Deprez, J. Guillauma, A. Corbier, J.-P. Vevert, M. Fortin and B. Heckmann, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2617.
15 C. Michaux, S. Rolin, J.-M. Dogna, F. Durant, B. Masereel, J. Delarge and J. Wouters, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1019.
16 S. Khelili, G. Leclerc, G. Faury and J. Verdetti, *Bioorg. Med. Chem.*, 1995, **3**, 495.
17 Y. Zohar, M. Einav, D. M. Chipman and Z. Barak, *Biochim. Biophys. Acta*, 2003, **1649**, 97.
18 C. King, *J. Org. Chem.*, 1060, **25**, 352.
19 H. Irie, M. Nishimura, M. Yoshidan and T. Ibuka, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1209.
20 J. Cervello and T. Sastre, *Synthesis*, 1990, 221.
21 A. Andreani, M. Rambaldi, A. Leoni, A. Localelli, F. Andreani and J.-C. Gehert, *Pharm. Acta Helv.*, 1996, **71**, 247.
22 Y. Ono, *Pure Appl. Chem.*, 1996, **68**, 367.
23 F. Bigi, R. Maggi and G. Sartori, *Green Chem.*, 2000, **2**, 140.
24 T. Mizuno, T. Kino, T. Ito and T. Miyata, *Synth. Commun.*, 2000, **30**, 3081.

25 N. Sonoda, T. Mizuno, S. Murakami, K. Kondo, A. Ogawa, I. Ryu and N. Kambe, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 452.
26 T. Mizuno, T. Iwai and Y. Ishino, *Tetrahedron*, 2005, **61**, 9157.
27 M. H. Ross, *Parasitology*, 1997, **114**, 137.
28 T. N. Z. Barragry, *Vet. J.*, 1984, **32**, 161.
29 N. Ni, T. Sanghvi and S. H. Yalkovsky, *Int. J. Pharm.*, 2002, **244**, 99.
30 J. Valdez, R. Cedillo, A. Hernandez-Campos, L. Yepez, F. Hernandez-Luis, G. Navarrete-Vazquez, A. Tapia, R. Cortes, M. Hernandez and R. Castillo, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2221.
31 E. Lacey, *Int. J. Parasitol.*, 1988, **18**, 885.
32 H.-J. Knolker, T. Braxmeier and G. Schlechtingen, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2497.
33 H.-J. Knolker, T. Braxmeier and G. Schlechtingen, *Synlett*, 1996, 502.
34 H.-J. Knolker and T. Braxmeier, *Tetrahedron Lett.*, 1996, **37**, 5861.
35 Y. Basel and A. Hassner, *J. Org. Chem.*, 2000, **65**, 6368.
36 M. Lamothe, M. Perez, V. Colovray-Gotteland and S. Halazy, *Synlett*, 1996, 507.
37 R. A. Batey, V. Santhakumar, Ch. Yoshina-Ishii and S. D. Taylor, *Tetrahedron Lett.*, 1998, **39**, 6267.
38 R. A. Batey, Ch. Yoshina-Ishii, S. D. Taylor and V. Santhakumar, *Tetrahedron Lett.*, 1999, **40**, 2609.
39 J. A. Grzyb and R. A. Batey, *Tetrahedron Lett.*, 2003, **44**, 7485.
40 H. Ishii, M. Goyal, M. Ueda and K. Takeuchi, *J. Mol. Catal. A: Chem.*, 1999, **148**, 289.
41 H. Y. Song, E. D. Park and J. S. Lee, *J. Mol. Catal. A: Chem.*, 2000, **154**, 243.
42 W. Aumuller and R. Weyer, *Ger. Pat. 10018*, 1961, *Chem. Abstr.*, 1961, **55**, 2460.
43 H. Ulrich, *Chem. Rev.*, 1965, **65**, 369.
44 B. M. Adger, S. Bradbury, M. Keating, Ch. W. Rees and M. T. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1975, 31–40.
45 R. Gompper and U. Wolf, *Liebigs Ann. Chem.*, 1979, 1388–1405.
46 A. S. Gorbesow, I. A. Wosmokow and Y. Muszkin, *Zh. Obshch. Khim.*, 1974, **44**, 2456–2462.
47 (*a*) M. Arnswald and W. P. Neumann, *Chem. Ber.*, 2000, **124**, 1997–2000; (*b*) J. H. M. Lange, H. K. A. C. Coden, H. H. van tuivenberg, K. Tipker, B. Stork, J. Hoogendoorn and Ch. G. Kruse, *J. Med. Chem.*, 2004, **47**, 627–643; (*c*) S. Bittner, Y. Assat, P. Krief, M. Pomerantz, B. T. Ziemnicka and Ch. G. Smith, *J. Org. Chem.*, 1985, **50**, 1712–1718.
48 (*a*) J. Howbert, C. S. Grossman, T. A. Crowell, B. J. Rieder, J. Aikins, S. M. Rinzel and G. C. Todd, *J. Med. Chem.*, 1990, **33**, 2393–2407; (*b*) E. Delacoux, G. Tsatsas and R. Delaby, *Bull. Soc. Chim. Fr.*, 1959, 1980–1983; (*c*) J. B. Pique, *ES Pat., 3*, 1966, **183**, 37; (*d*) G. E. Holland, D. A. Jaeger, R. L. Wagner, G. D. Laubach, W. M. McLamore and S. Y. P'an, *J. Med. Pharm. Chem.*, 1961, **3**, 99–110.

Catalytic oxidation of mercaptans by bifunctional catalysts composed of cobalt phthalocyanine supported on Mg–Al hydrotalcite-derived solid bases: effects of basicity

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Received 7th March 2006, Accepted 12th June 2006
First published as an Advance Article on the web 20th June 2006
DOI: 10.1039/b603461f

The oxidation of 1-octanethiol to corresponding disulfide as a model reaction for mercaptan sweetening was examined on the bifunctional catalysts prepared by supporting cobalt phthalocyanine tetrasulfonate (CoPcTs) on mixed-oxide solid bases (designated as Mg(Al)O) derived from thermal decomposition of Mg–Al hydrotalcites with five Mg/Al molar ratios of 3.0, 4.9, 6.5, 9.0 and 13.2, and for comparison on Al_2O_3, MgO and K^+-modified Mg(Al)O (Mg/Al = 3.0). For the five Mg(Al)O samples, at a similar CoPcTs dispersion, the oxidation rates increased in parallel with the number of the basic sites provided by the support surfaces, but their rates were greater than those of the corresponding MgO and K^+-modified Mg(Al)O samples although MgO and K^+-modified Mg(Al)O possessed more basic sites with stronger base strength compared to Mg(Al)O, showing the dependence of the oxidation rates not only on the numbers of the basic sites, but also on their nature and strength. In combination of the *in situ* infrared results for 1-hexanethiol adsorption on Mg(Al)O, effects of titration of the basic sites with CO_2, BF_3 and H_2O on the reaction rates for CoPcTs/Mg(Al)O (Mg/Al = 3.0) led to the identification of the basic OH^- rather than O^{2-} ions as the active basic sites for the mercaptan oxidation. 1-propanethiol temperature-programmed desorption showed the effects of the base strength on the strength of the mercaptan adsorption on the Co^{2+} site of CoPcTs as a result of the effects on the electron density of the Co^{2+} site. Such effects led to the poor activities for the MgO and K^+-modified Mg(Al)O samples, due to their strong base strength and consequently weaker mercaptan adsorption and activation on the Co^{2+} sites. It is thus clear that the OH^- basic sites and medium base strength are required for the mercaptan oxidation, which provides the basis for the rational design of more efficient solid bases for the sweetening process.

1. Introduction

Mercaptans (RSH) distribute in petroleum products, and their presence, even in very small quantities, gives rise to an unpleasant odor and corrosiveness.[1] Their removal (usually referred to as "sweetening") is thus necessary, leading to extensive efforts in developing efficient sweetening processes. Among them, the mercaptan oxidation (Merox) process developed by UOP has been most widely practiced in the petroleum refining industry, which involves catalytic oxidation of the mercaptans to innocuous disulfides with air by cobalt phthalocyanines in the presence of caustic soda as a co-catalyst.[1] However, the use of caustic soda in this process led to its environmental and economic disadvantages in the refinery because the spent caustic soda is recognized as a hazardous waste, and its disposal is becoming more difficult and expensive due to the steady tightening of environmental regulations worldwide.[2,3] The ideal solution to this problem is to substitute solid bases for caustic soda to develop a more environmentally friendly effluent-free process for the mercaptan sweetening.

Mixed Mg–Al oxides (designated as Mg(Al)O) derived from thermal decomposition of hydrotalcites, which are layered double hydroxides, have been regarded as promising solid bases with controllable basicity through the control of their chemical compositions and thermal treatment parameters, *etc.*[4–8] These solids have been used in a variety of reactions typically catalyzed by aqueous bases, such as aldol condensations,[6,9] alkylations,[10] Knoevenagel condensations,[11] and olefin isomerization.[9] Holmgren *et al.*[2,12] and Liu *et al.*[13–15] recently reported that Mg(Al)O-supported cobalt phthalocyanine bifunctional catalysts, which possess Co^{2+} oxidation sites and Mg(Al)O base sites in cooperative interaction, can effectively oxidize mercaptans to disulfides. But for these catalysts, the effects of basic properties of the Mg(Al)O materials including the number, nature and strength of the basic sites have not been examined in detail. Elucidation of these effects will be relevant to the rational design and control of the basicity required for the mercaptan oxidation, leading to the development of new solid base catalysts efficient for the mercaptan sweetening. Hence, in this work we report a systematic study on the correlation between the mercaptan

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oxidation activities and the basicity of the Mg(Al)O materials, from which the requirements of the basic sites for the target reaction are clarified.

2. Experimental

Catalyst preparation

Tetrasodium salt of cobalt(II) 4′,4″,4‴,4⁗-tetrasulfophthalocyanine ($Co(II)Pc(SO_3Na)_4$, designated as CoPcTs) was prepared by sulfonation of CoPc with oleum (fuming sulfuric acid).[13] To ~30% oleum, cobalt(II) phthalocyanine (2 g) was added at ~273 K with agitation in flowing N_2. After cobalt(II) phthalocyanine was dissolved, the temperature was slowly raised to 303–308 K in about 3 h and agitated at the constant temperature for 48 h. The resulting solution was then added carefully to a mixture of ice and water in flowing N_2, and blue precipitates concurrently appeared. Afterwards, the blue precipitates were filtered and washed thoroughly with cold water, followed by dissolving in an aqueous solution of NaOH. To this solution, equal volume of methanol was added and then Na_2SO_4 precipitated. This step was repeated several times in order to remove all Na_2SO_4 from the solution. $Co(II)Pc(SO_3Na)_4$ (CoPcTs) was then obtained by distilling the filtrate under reduced pressure, followed by re-crystallization with methanol and acetone, washing with anhydrous ethanol and drying at 363 K under vacuum.

Five Mg–Al hydrotalcite samples were prepared by coprecipitation of an aqueous solution containing $Mg(NO_3)_3{\cdot}6H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$ with a solution of KOH and K_2CO_3.[5,7] The Mg/Al molar ratios were varied from 3 to 5, 7, 10 and 15 by keeping a constant cation (Mg^{2+} + Al^{3+}) concentration of 1 M, and the Al^{3+}/CO_3^{2-} molar ratios were maintained at 2. The coprecipitation was carried out at 303–323 K and a pH of 8–10. After the coprecipitation, the resulting white slurry was stirred at 303–323 K for another 4 h. The precipitate was then filtered and thoroughly washed with hot deionized water to remove K^+, and subsequently dried in air at 353 K for 12 h. The ICP analysis results showed that the Mg/Al molar ratios for the five samples were 3.0, 4.9, 6.5, 9.0 and 13.2, respectively, which were very similar to the ratios in the coprecipitation solutions. For comparison, $Mg(OH)_2$ and $Al(OH)_3$ were also prepared by coprecipitation of an aqueous solution of $Mg(NO_3)_3{\cdot}6H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$ with KOH solution, respectively.

The Mg–Al mixed oxides (Mg(Al)O) were obtained by calcination of the five hydrotalcites in air typically at 723, 773 and 823 K for 8 h,[7] and they were denoted as Mg(Al)O-3, Mg(Al)O-4.9, Mg(Al)O-6.5, Mg(Al)O-9, and Mg(Al)O-13.2, respectively, where the numbers represents the measured Mg/Al molar ratios. K^+-modified Mg(Al)O-4.9 (denoted as K^+-Mg(Al)O-4.9) was prepared by incipient wetness impregnation of Mg(Al)O-4.9 with an aqueous KOH solution containing 0.15 mmol K^+ per gram sample, followed by successive drying at 353 K for 6 h and at 393 K for 2 h, and finally calcination at 773 K for 8 h.

The supported $Co(II)Pc(SO_3Na)_4$ catalysts were prepared by incipient wetness impregnation of fresh Mg(Al)O oxides, Al_2O_3 and MgO with degassed anhydrous methanolic solutions of $Co(II)Pc(SO_3Na)_4$ (CoPcTs) in dry N_2 flow at 298 K for 3 h, followed by drying under vacuum at 323 K for 2 h. The catalysts typically contained 1 wt% (*i.e.* 1.02 μmol) CoPcTs in this work. Before use, all these oxides and supported catalysts were kept free of any contact with moisture and air.

Catalyst characterization

FT-IR spectra for 1-hexanethiol and CO_2 adsorption were recorded on a Perkin-Elmer spectrometer equipped with a MCT detector with a resolution of 4 cm^{-1}. Mg(Al)O samples were pressed into thin self-supporting wafers and placed in a quartz cell with CaF_2 windows. The samples were pretreated in the cell at 773 K for 1 h under vacuum and then cooled to 298 K under vacuum. Afterwards, the samples were exposed to 1-hexanethiol vapor, CO_2 or their mixture at 298 K. All the spectra were obtained as difference spectra by subtracting the background spectrum of the oxide samples, *i.e.* the spectrum recorded just after their pretreatments, from the obtained spectra.

1-propanethiol temperature-programmed desorption (TPD) measurements were performed in a flow unit equipped with a TCD detector. Samples (0.1 g) were placed in a quartz cell and pretreated at 623 K for 3 h in dry He flow (20 cm^3 min^{-1}). After the samples were cooled to 298 K, they were exposed to controlled amounts of 1-propanethiol in a dry He flow (20 cm^3 min^{-1}). After flushing with He flow (20 cm^3 min^{-1}) at 298 K, the samples were heated to 623 K at 10 K min^{-1} in flowing He (20 cm^3 min^{-1}), and the desorption of 1-propanethiol was measured using the TCD detector.

Catalytic mercaptan reactions

The catalytic properties of the catalysts were studied using the oxidation of 1-octanethiol as a model reaction. The 1-octanethiol oxidation reactions were carried out in a thermostatted double-walled glass flask equipped with a high-speed stirrer.[7,16] 0.06–0.1 g of catalysts containing 0.612–1.02 μmol CoPcTs, 5 ml of dry n-octane and dry oxygen were introduced to the reaction flask. After the injection of 1 ml of 1-octanethiol (Fluka, >97.%), the reaction started at 308 (±0.1) K under constant oxygen pressure (1 atm), and the oxygen depletion was monitored with a gas burette to evaluate the catalytic activities and initial reaction rates (ml min^{-1} μmol-Co^{-1}). The reaction solutions were analyzed by GC-MS, and $C_8H_{17}SSC_8H_{17}$ was the only 1-octanethiol oxidation product. No H_2O_2 accumulation was detected. Therefore, the conversion of 1-octanethiol proceeds according to the following equation, 4 $C_8H_{17}SH + O_2 \rightarrow 2\ C_8H_{17}SSC_8H_{17} + 2\ H_2O$. Re-use of the catalysts did not show significant loss of their activities.

3. Results and discussion

Table 1 shows the initial 1-octanethiol reaction rates at 308 K for the bifunctional catalysts composed of CoPcTs supported on different Mg–Al mixed oxides (Mg(Al)O), MgO and Al_2O_3 with similar CoPcTs dispersions. No 1-octanethiol conversions were detected in the absence of CoPcTs or the basic oxide supports, indicating that both the Co^{2+} oxidation sites and the basic sites are required for the mercaptan oxidation. For the

Table 1 Initial reaction rates of different supported CoPcTs catalysts for the 1-octanethiol oxidation at 308 K and the basicity of the different oxide supports[a]

Support	Rate/ml min^{-1} μmol^{-1} Co	Basic site number/$\mu mol\ g^{-1}$		
		Total	OH^- sites	O^{2-} sites
Mg(Al)O-3	3.2	271.6	95.6	176.0
Mg(Al)O-4.9	2.8	224.8	78.2	146.6
Mg(Al)O-6.5	2.6	199.8	67.1	132.7
Mg(Al)O-9	1.6	172.2	56.8	115.4
Mg(Al)O-13.2	1.4	164.5	53.8	110.7
Mg(Al)O-3[b]	2.9	151.4	54.5	96.9
Mg(Al)O-3[c]	2.5	204.0	66.2	137.8
K^+-Mg(Al)O-3	1.0	310.0	49.1	260.9
MgO	1.3	288.1	80.0	208.1
Al_2O_3	0.6	134.4	68.2	66.2

[a] The oxide supports were typically obtained after thermal decomposition of the corresponding hydroxides at 773 K. [b] The thermal decomposition temperature was 723 K. [c] The thermal decomposition temperature was 823 K.

series of Mg(Al)O-supported CoPcTs samples, the reaction rates increased from 1.4 to 3.2 ml min^{-1} μmol^{-1} Co with decreasing Mg/Al molar ratios from 13.2 to 3, and were higher than the rates for the MgO and Al_2O_3 samples. Modification of the Mg(Al)O-4.9 catalyst with K^+ led to a decrease in the reaction rate by a factor of about three (1.0 *vs.* 2.8 ml min^{-1} μmol^{-1} Co).

In our previous work,[7] we have examined the basicity of the Mg(Al)O solid bases by stepwise temperature-programmed desorption of CO_2 and infrared spectroscopy of adsorbed CO_2 and $B(OCH_3)_3$. The basicity of Mg(Al)O depends on the Mg and Al contents of the hydrotalcite precursors and the thermal decomposition temperatures. At a given temperature, *e.g.* 773 K, the number of the basic sites (per gram or per surface area) increases with decreasing the Mg/Al molar ratios in the range 3–13.2 studied; the number increases with increasing the calcination temperature and reaches the maximum values at 773 K and then declines at higher temperatures, as summarized in Table 1. Conversely, the base strength increases with increasing the Mg/Al ratios and the decomposition temperatures for all the Mg(Al)O samples employed in this work. The number and strength of the basic sites for these mixed oxides are in between those for MgO and Al_2O_3. Modification of the Mg(Al)O sample with K^+ significantly increases the basic site number and strength. On these oxide surfaces, two types of the basic sites are identified, which include weaker Brønsted OH^- and stronger Lewis O^{2-} sites.

By comparing the basicity of the oxide supports and the reaction rates shown in Table 1, it was found that the reaction rates increased almost linearly with increasing number of basic sites for the five Mg(Al)O-supported CoPcTs catalysts. But the rates did not always change in parallel with the basic site numbers. For example, compared to Mg(Al)O-4.9, MgO and K^+-Mg(Al)O-4.9 possessed more basic sites (per gram) with higher base strength, but they exhibited surprisingly lower reaction rates. This phenomenon was also observed for the Mg(Al)O samples decomposed at different temperatures. For Mg(Al)O-3, decomposition at 823 K led to superior basicity, but also to an inferior reaction rate compared to decomposition at 723 K. These observed basicity effects reveal that the

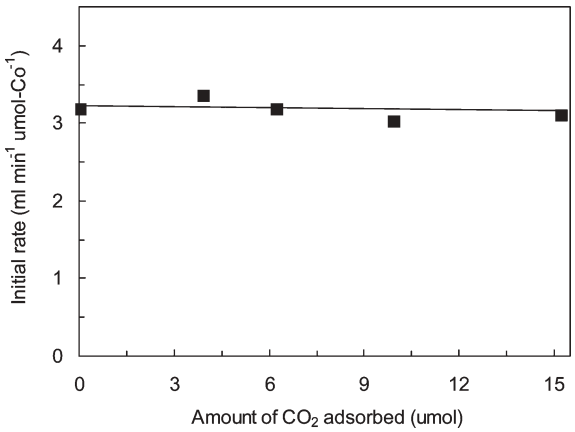

Fig. 1 Initial 1-octanethiol oxidation rates at 308 K as a function of the amount of CO_2 adsorbed on the supported CoPcTs/Mg(Al)O-3 catalyst.

reaction rates are dependent also on the nature and strength of the basic sites, not only on their total numbers.

In order to elucidate the nature of the basic sites, the effects of addition of CO_2, H_2O and BF_3 as the basic site titrants on the mercaptan oxidation activities were examined. It is known that CO_2 strongly interacts only with Lewis O^{2-} basic sites to block these stronger sites, and H_2O adsorption on the O^{2-} sites leads to the formation of new basic OH^- sites *via* the interaction between O^{2-} and H_2O,[17] whereas BF_3 as a strong Lewis acid can react with both the O^{2-} and OH^- sites to "kill" them.[7] Fig. 1 shows the reaction rates on the Mg(Al)O-3 supported CoPcTs catalysts before and after adsorption of various amount of CO_2, approximately 3.9, 6.2, 9.9, and 15.2 μmol, where 15.2 μmol corresponds to the amount of CO_2 occupying all the basic sites on Mg(Al)O-3 (*ca.* 60 mg). The rates were constant with variation of the amount of adsorbed CO_2. Upon addition of BF_3, however, the reaction rates, as shown in Fig. 2, significantly decreased, and approached zero as more than 20 μmol BF_3 was added, corresponding to blocking of all the basic sites (~16 μmol). These results show that the base function of the catalysts is vital for the mercaptan oxidation, but the active basic sites involve the OH^- ions

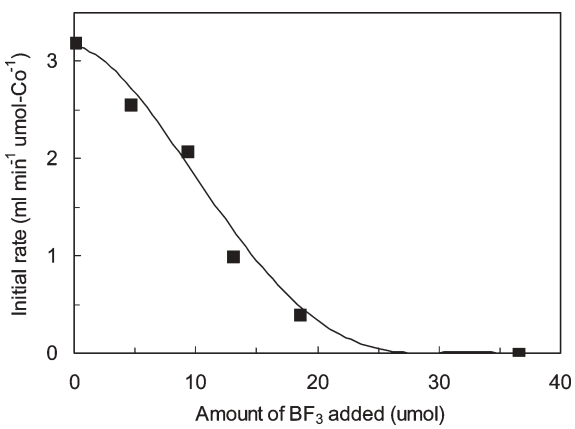

Fig. 2 Initial 1-octanethiol oxidation rates at 308 K as a function of the amount of BF_3 adsorbed on the supported CoPcTs/Mg(Al)O-3 catalyst.

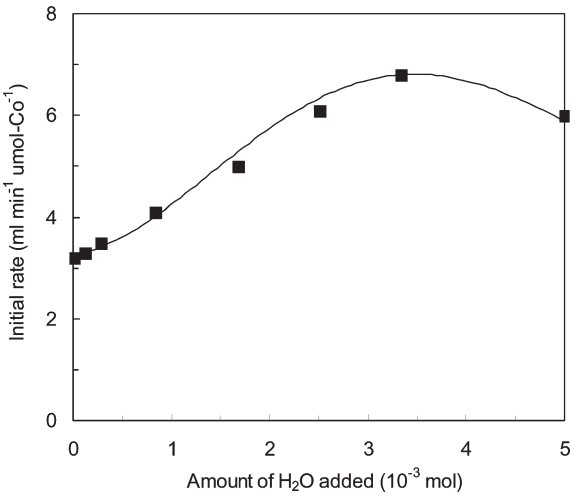

Fig. 3 Initial 1-octanethiol oxidation rates at 308 K as a function of the amount of H_2O adsorbed on the supported CoPcTs/Mg(Al)O-3 catalyst.

rather than the O^{2-} ions. This is consistent with the effects of H_2O addition. As shown in Fig. 3, adsorption of H_2O on the CoPcTs/Mg(Al)O-3 catalyst led to a marked increase in the reaction rate from 3.2 ml min^{-1} μmol^{-1} Co in the absence of H_2O to a maximum value of 6.8 ml min^{-1} μmol^{-1} Co at 3.3 mmol H_2O, as the result of the newly formed OH^- basic sites upon the H_2O adsorption on the surface O^{2-} basic sites. Excess H_2O however decreased the reaction rates, most likely due to the restructuring of the Mg(Al)O surfaces to the hydrotalcite structures that resulted in losing part of the basic sites.[4,13]

The involvement of the OH^- basic sites in the mercaptan oxidation was further confirmed by FT-IR spectroscopy for 1-hexanethiol adsorption on Mg(Al)O. Due to their different base strengths, the interaction of the basic OH^- and O^{2-} sites with 1-hexanethiol would differently affect the vibration of the S–H bond, leading to the difference in the wavenumbers of ν_{S-H} for the adsorbed mercaptan species. But the IR band of ν_{S-H} is very weak, which indicates that it is unreliable to distinguish the basic OH^- and O^{2-} sites based on the difference in the wavenumbers of ν_{S-H}. For this purpose, we probed the co-adsorption of CO_2 and 1-$C_6H_{13}SH$. Fig. 4 shows the FT-IR spectra for 1-$C_6H_{13}SH$ adsorption, followed by CO_2 adsorption on Mg(Al)O-4.9 at 298 K. Upon the 1-$C_6H_{13}SH$ adsorption, three bands, corresponding to the bending vibrations of C–H and S–C–H bonds, respectively, appeared at 1463, 1382, and 1298 cm^{-1} in the range 1800–1200 cm^{-1} at the expense of the surface basic OH^- sites, as reflected by the reverse ν_{O-H} band at 3744 cm^{-1} (curve a). This shows the strong interaction between 1-$C_6H_{13}SH$ and the basic OH^- sites. Subsequent adsorption of CO_2 led to the appearance of three new bands at 1601 (s), 1410 (w) and 1310 cm^{-1} in the range 1800–1200 cm^{-1} (curve b). The bands at 1410 and 1310 cm^{-1} are assigned to the symmetric stretching mode of unidentate carbonate and bidentate carbonates, respectively, and the most intense band at 1601 cm^{-1} is tentatively attributed to the asymmetric stretching mode of these carbonates.[18,19] These carbonates

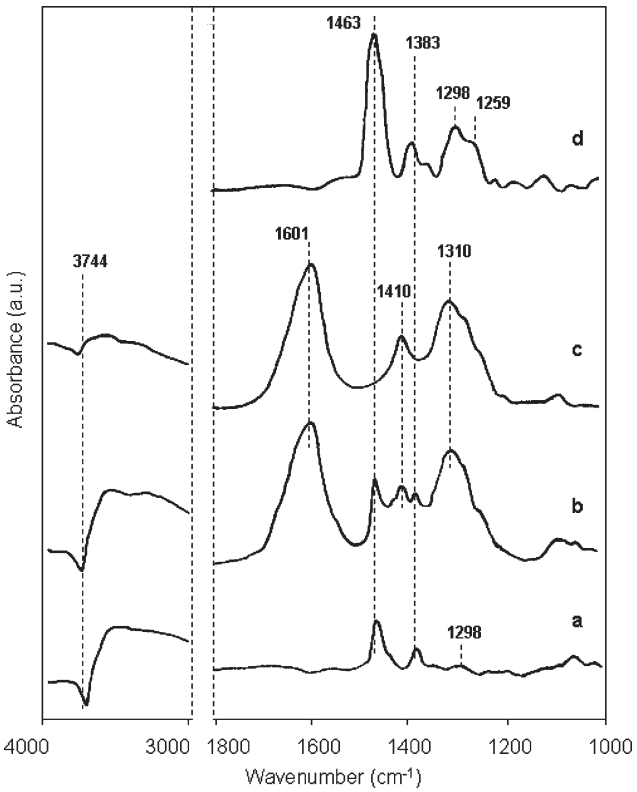

Fig. 4 FT-IR spectra for (a) 1-hexanethiol adsorption, and (b) subsequent adsorption of CO_2 on Mg(Al)O-4.9, and (c) for difference of (b) − (a), as well as (d) for gas phase 1-hexanethiol.

were formed by adsorption of CO_2 on the basic O^{2-} anions,[18,19] indicating that 1-$C_6H_{13}SH$ did not occupy the O^{2-} sites or at least its adsorption on the O^{2-} sites was weaker than CO_2 adsorption. After the subsequent CO_2 adsorption, the 1-$C_6H_{13}SH$ bands remained essentially unchanged, which can be seen more clearly from the difference spectrum of b and a as shown in Fig. 4 (curve c). This indicates even no weak adsorption of 1-$C_6H_{13}SH$ on the O^{2-} sites, otherwise the 1-$C_6H_{13}SH$ bands would be seen from curve c. No characteristic bands of surface bicarbonate species were detected around 3620, 1660 and 1220 cm^{-1} upon the subsequent CO_2 adsorption, which show no OH^- basic sites to interact with CO_2 to form bicarbonate[7,18,19] after the 1-$C_6H_{13}SH$ adsorption. Similar results were obtained with other experiments done by CO_2 adsorption and subsequent mercaptan adsorption, and by concurrent adsorption of CO_2 and mercaptan (spectra not shown). These results clearly demonstrate that mercaptan interacts with only the OH^- sites, not the O^{2-} sites. Such basic OH^- site requirement is also observed for aldol addition of acetone, and aldol condensation of acetone and benzaldehyde on MgO and Mg(Al)O.[6,17]

Fig. 5 shows the 1-C_3H_7SH TPD profiles for Mg(Al)O-4.9, CoPcTs/Mg(Al)O-4.9, CoPcTs/MgO, and CoPcTs/Al_2O_3 for getting insight into the influences of the basicity on the mercaptan adsorption on the Co^{2+} sites of the supported CoPcTs molecules. The amounts of 1-C_3H_7SH introduced were controlled to the point where the1-C_3H_7SH adsorption on the supports reached almost its lowest levels but without being detrimental to the adsorption on the Co^{2+} sites, as

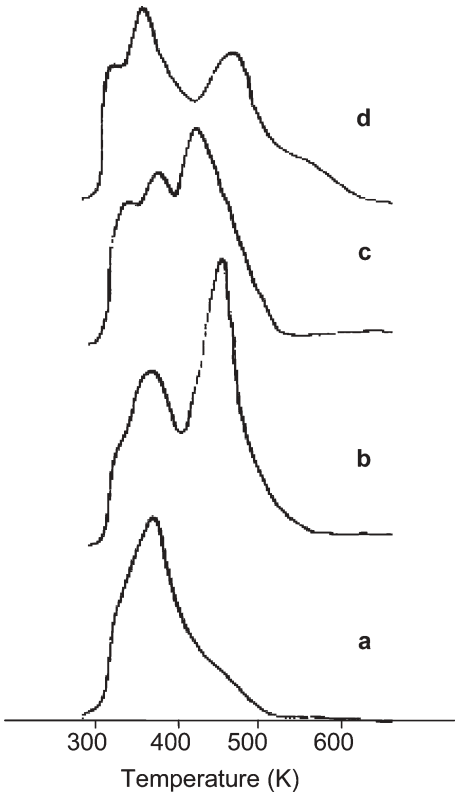

Fig. 5 1-Propanethiol TPD profiles for Mg(Al)O-4.9 (a), and CoPcTs supported on Mg(Al)O-4.9 (b), MgO (c) and Al_2O_3 (d).

reported by Fischer, *et al*[20] with cobalt phthalocyanines supported on SiO_2. For the fresh Mg(Al)O-4.9 support, an intense peak with two weak shoulders appeared around 358 K, 329 K and 441 K, respectively, indicating the adsorption of 1-C_3H_7SH on the basic sites with different strength. Three desorption peaks were also detected for the CoPcTs/Mg(Al)O-4.9 sample after contact with controlled amount of 1-C_3H_7SH, which appeared around 327 K, 358 K and 461 K. By comparing these two TPD curves, the intense peak at 461 K can be attributed to 1-C_3H_7SH desorption from the Co^{2+} sites on the Mg(Al)O-4.9 support. This peak shifted from 461 K to 475 K and 433 K as the support changed from Mg(Al)O-4.9 to Al_2O_3 and MgO, respectively. For CoPcTs/Al_2O_3, there is an additional shoulder around 531 K. Measured 1-C_3H_7SH/Co^{2+} ratios for these three samples were in the range 0.79–0.82, corresponding to adsorption of roughly one mercaptan molecule per one Co^{2+} site. These results reflect the similar CoPcTs dispersions on the three supports.

1-C_3H_7SH adsorbs on the CoPcTs sites *via* coordination of the donating sulfur of the –SH group to the accepting Co^{2+} ion forming a Co–S(H)C_3H_7-1 bond. The strength of this bond depends on the electron density of the cobalt sites, which directly affects the thermal desorption of 1-C_3H_7SH from the cobalt sites. Basicity of a sample reflects its electron-donation property.[18] Compared to Al_2O_3 and Mg(Al)O, MgO possesses higher base strength, and tends to interact more strongly with the Co^{2+} sites, leading to the higher electron density of the Co^{2+} sites and thus the weaker adsorption of 1-C_3H_7SH on the Co^{2+} sites on MgO than on Mg(Al)O and Al_2O_3. This is consistent with the observed shift of the 1-C_3H_7SH desorption peak (on the Co^{2+} sites) to the lower temperatures with changing the support from weak basic Al_2O_3 to stronger basic Mg(Al)O and to MgO, as shown in Fig. 5. Such effects of the basicity on the mercaptan adsorption strength will finally affect the activation and conversion of mercaptan.

According to the mechanism for the mercaptan (RSH) oxidation on these Mg(Al)O-supported CoPcTs catalysts, RSH conversion to disulfide (RS-SR) proceeds *via* the coordination of RSH to the Co^{2+} sites to form an $RS^{\bullet}$ radical, which then interacts with RS^- anion formed by reaction of RSH with the basic OH^- sites to form coordinated $RS^{\bullet -}$ species as the rate-limiting step, followed by its desorption as RS-SR from the reduced Co^+ sites.[21] Accordingly, the adsorption strength of RSH on the Co^{2+} sites influences the $RS^{\bullet}$ radical formation and its subsequent conversions; adsorption that is too weak does not favor the $RS^{\bullet}$ radical formation, while adsorption that is too strong makes the following steps (*e.g.* the RSSR desorption) unfavorable to occur. Therefore in this work, optimal adsorption strength, imposed by optimal base strength, is required for efficiently achieving catalytic turnovers. The poor activity of CoPcTs/MgO compared to CoPcTs/Mg(Al)O, as shown in Table 1, is apparently because of the stronger basicity of MgO that led to the weaker adsorption and activation of 1-$C_8H_{17}SH$ on the supported Co^{2+} sites, despite the greater amount of the basic OH^- sites on MgO compared to on most of the Mg(Al)O supports, as discussed above. This explanation is applicable to understanding the lower activity for the sample using the Mg(Al)O support calcined at 823 K, relative to the one calcined at 723 K (Table 1). Such requirements of nature and strength of the basic sites, *i.e.* OH^- basic sites and medium base strength, provide a new insight into the understanding of the solid base-based catalysts for the mercaptan oxidation, which will be helpful to the rational design of more efficient catalysts leading to their application in the sweetening process. Such understanding shows the advantages of the catalyst systems in this work, since unlike the O^{2-} sites and strong base strength, no special cares, especially about poisoning of CO_2 and H_2O (an unavoidable product), need to be taken. Such simple site requirements are indeed desired for an environmentally benign commercial process.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant no. 20573004, 20443010) and China Petrochemical Corporation (SINOPEC). The authors thank Professors X. Yang, C. Li and Q. Xin, and Dr J. Liu for their assistance and helpful discussions.

References

1 B. Basu, S. Satapathy and A. K. Bhatnagar, *Catal. Rev.*, 1993, **35**, 571.
2 J. J. Alcaraz, B. J. Arena, R. D. Gillespic and J. S. Holmgren, *Catal. Today*, 1998, **43**, 89.
3 D. L. Holbrook, B. J. Arena, T. Verachtert and J. C. Bricker, *NRPA Annu. Meet.*, 1993.
4 F. Cavani, F. Trifiro and A. Vaccari, *Catal. Today*, 1991, **11**, 173.

5 A. L. McKenzie, C. T. Fishel and R. J. Davis, *J. Catal.*, 1992, **138**, 547.
6 D. Tichit, M. H. Lhouty, A. Buida, B. H. Chiche, F. Figueras, A. Auroux, D. Bartalini and E. Garrone, *J. Catal.*, 1995, **151**, 50.
7 H. C. Liu, X. Y. Yang, G. P. Ran, E. Z. Min, J. K. Liu, P. L. Ying, Q. Xin and C. Li, *Chin. J. Chem.*, 1999, **17**, 319.
8 J. I. Di Cosimo, C. R. Apesteğua, M. J. L. Gines and E. Iglesia, *J. Catal.*, 2000, **190**, 261.
9 W. T. Rechle, *J. Catal.*, 1985, **94**, 547.
10 S. Velu and C. S. Swamy, *Appl. Catal.*, 1994, **119**, 241.
11 A. Corma, S. Iborra, J. Primo and F. Rey, *Appl. Catal.*, 1994, **114**, 215.
12 R. D. Gillespic, J. C. Bricker, B. J. Arena and J. S. Holmgren, US Patent 5413701, 1995.
13 H. Liu, G. Ran, E. Min and X. Yang, *Chin. J. Mol. Catal.*, 1998, **12**, 221.
14 H. Liu, X. Yang, G. Ran and E. Min, *Acta Phys.-Chim. Sin.*, 1999, **15**, 918.
15 H. Liu, X. Yang, G. Ran and E. Min, *J. Chem. Res.*, 2000, 294.
16 J. H. Schutten and J. Zwart, *J. Mol. Catal.*, 1979, **5**, 109.
17 G. Zhang and K. Tanabe, *Appl. Catal.*, 1988, **36**, 189.
18 J. A. Lercher, C. Colombier and H. Holler, *J. Chem. Soc., Faraday Trans.*, 1984, **80**, 294.
19 J. V. Evans and T. L. Whateley, *Trans. Faraday Soc.*, 1967, **63**, 2769.
20 H. Fischer and G. Shultz-Ekloff, *Langmuir*, 1992, **8**, 2720.
21 H. Liu and E. Min, *to be submitted*.

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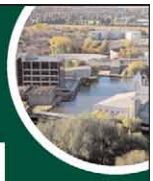

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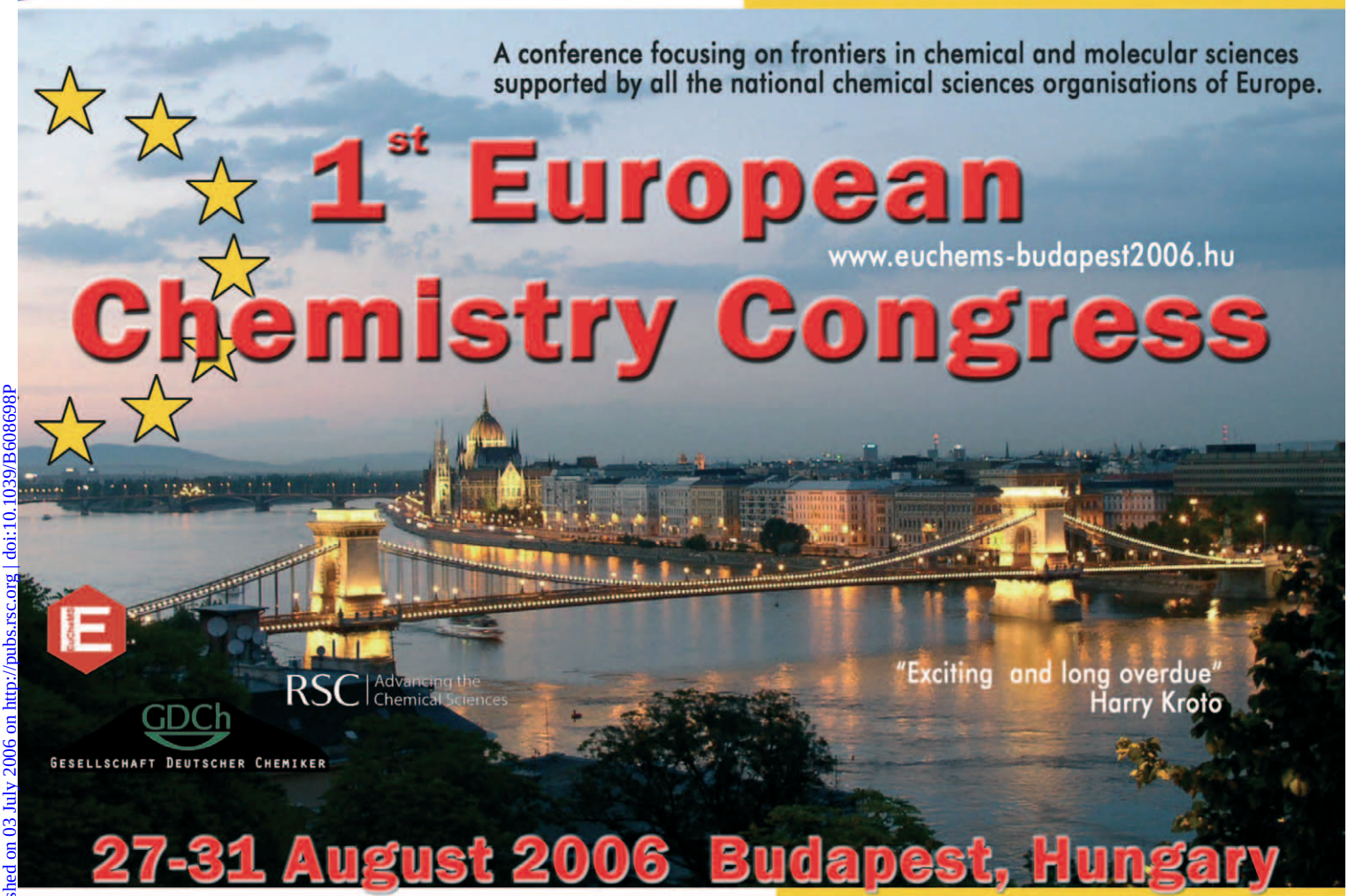

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