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# Green Chemistry

Cutting-edge research for a greener sustainable future

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Volume 7 Number 1 | January 2005 | Pages 1–48

ISSN 1463-9262

RSC | Advancing the Chemical Sciences

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1463-9262(2005)7:1;1-F

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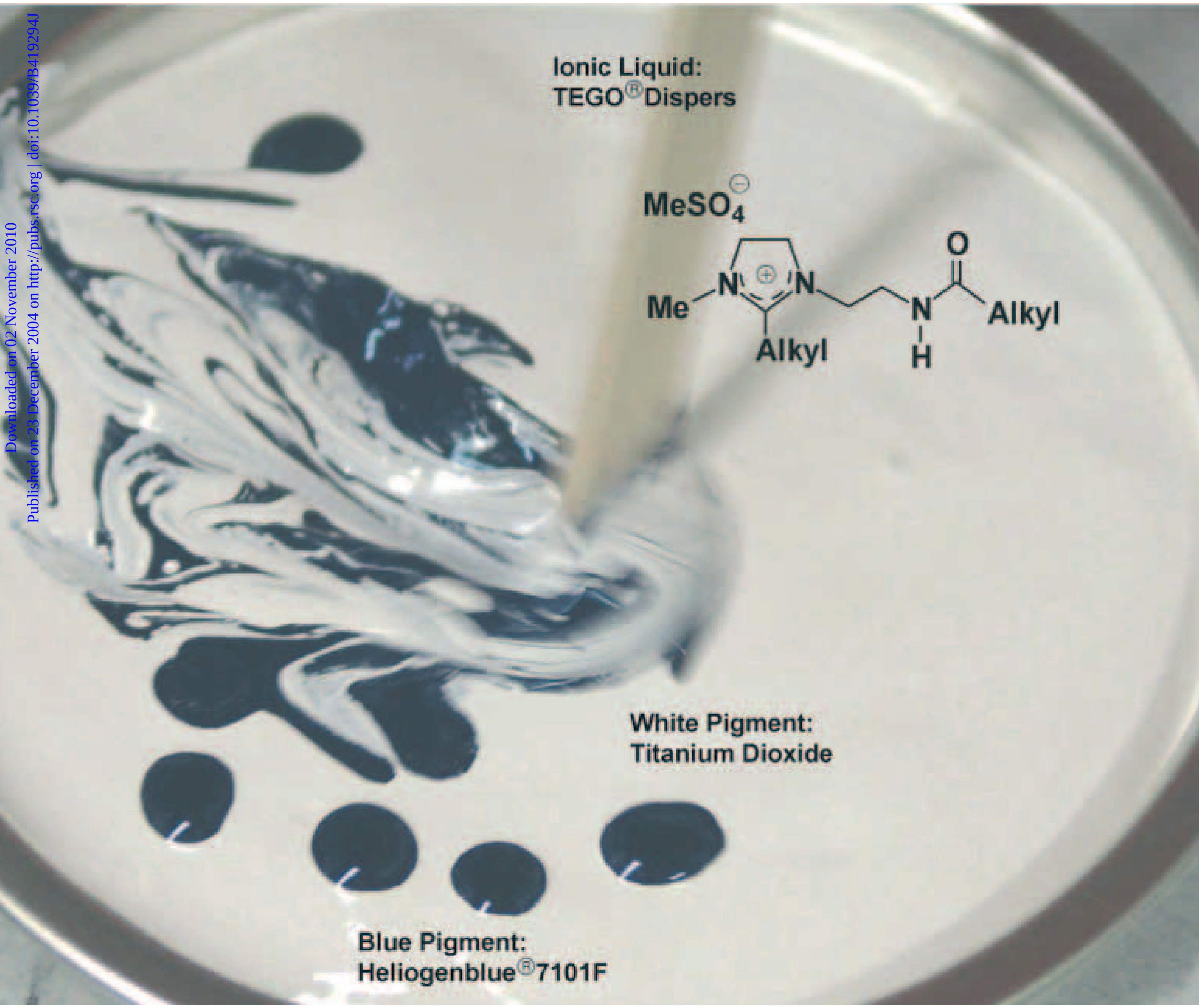

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## IN THIS ISSUE

ISSN 1463-9262 CODEN GRCHFJ 7(1) 1–48 (2005)

**Cover**
Water Flea (*Daphnia magna*) in a water drop held by a grass head. The development and application of ionic liquids in Green Chemistry is prolific. Described within is the study of the biodegradation and toxicology of ionic liquids with the propensity to degrade in the environment. The water flea is an important assay for the toxicity of ionic liquids. (Photo from Warren Photographic Digital Image Library http://www.warrenphotographic.co.uk).

**Cover**
The photograph (by Angela Rüttgerodt) shows the tinting of a white base paint with a universal pigment paste (blue) using an ionic liquid as compatibilizer. Ionic liquids provide a cost-wise attractive solution to the paint and coating industry for the tinting of problematic solvent-based paints and coatings and will help to reduce the consumption of VOCs in the future.

## CHEMICAL TECHNOLOGY

T1

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

**Chemical Technology**
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### Green Chemistry 2005: new look, new people, new chances

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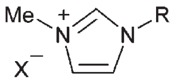
### Biodegradable ionic liquids Part II. Effect of the anion and toxicology

M. Teresa Garcia,* Nicholas Gathergood and Peter J. Scammells*

The effect of the counter-ion on IL biodegradability has been studied in two IL test sets. A preliminary evaluation of IL toxicity has also been conducted.



R = butyl,
propoxycarbonylmethyl

# Green Chemistry

## Cutting-edge research for a greener sustainable future

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Green Chemistry focuses on cutting-edge research that attempts to reduce the environmental impact of the chemical enterprise by developing a technology base that is inherently non-toxic to living things and the environment.

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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 accompanied by payment should be sent directly to Portland Customer Services, Commerce Way, Colchester, Essex, CO2 8HP. Tel +44 (0) 1206 226050; E-mail sales@rscdistribution.org

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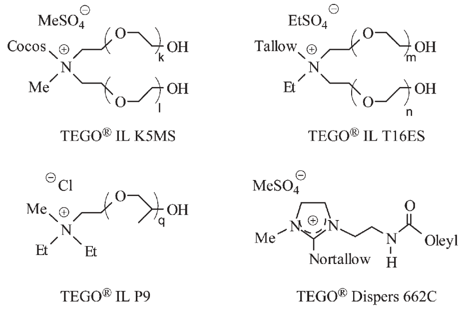
## Industrial application of ionic liquids as performance additives

Bernd Weyershausen* and Kathrin Lehmann

The use of ionic liquids as secondary dispersants in combination with water-based pigment pastes is introduced. This application represents a significant advancement concerning the contribution to the chemical industry's initiatives "sustainable development" and "responsible care" and will help to reduce the consumption of VOCs in the future.



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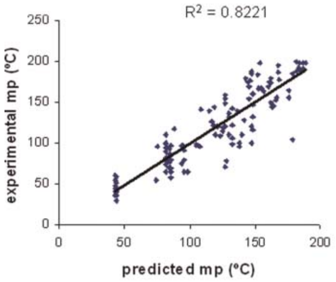
## Estimation of melting points of pyridinium bromide ionic liquids with decision trees and neural networks

Gonçalo Carrera and João Aires-de-Sousa*

Regression trees were automatically built to predict the melting point of 126 pyridinium bromides ($R^2 = 0.822$). This is a relevant method for designing new ionic liquids (potential green solvents).



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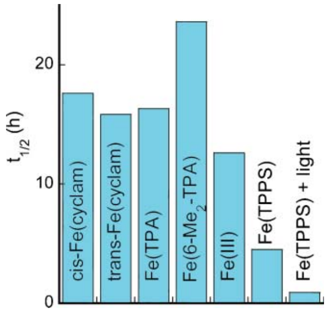
## Oxidation of 2,4,6-trichlorophenol by hydrogen peroxide. Comparison of different iron-based catalysts

Gábor Lente* and James H. Espenson

Extending the concept of atom utilisation for complex reactions, stoichiometric and kinetic efficiencies were defined for the title reaction and measured systematically using six different iron-based catalysts.



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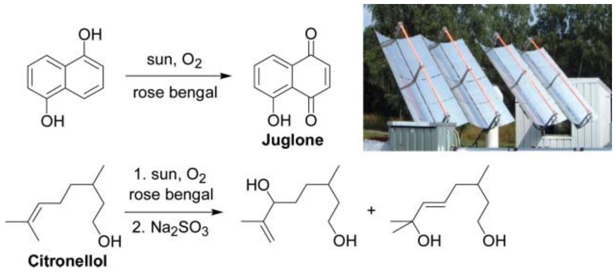
## Green photochemistry: solar photooxygenations with medium concentrated sunlight

Michael Oelgemöller,* Christian Jung, Jürgen Ortner, Jochen Mattay and Elmar Zimmermann

This article describes solar photooxygenations with moderately concentrated sunlight for the production of fine chemicals. Complete conversions were achieved on multigram to kilogram scales in relatively short illumination times thus demonstrating the potential of this application.



## PAPERS

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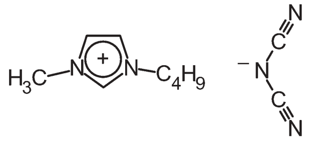

### Room-temperature ionic liquids that dissolve carbohydrates in high concentrations

Qingbin Liu, Michiel H. A. Janssen, Fred van Rantwijk and Roger A. Sheldon*

The use of carbohydrates as renewable feedstocks is greatly hampered by their low solubility in any solvent but water. Ionic liquids that contain the dicyanamide ion (dca) dissolve approx. 200 g $L^{-1}$ of glucose, sucrose and cyclodextrin. *Candida antarctica* lipase B mediated the esterification of sucrose with dodecanoic acid in [BMIm][dca].

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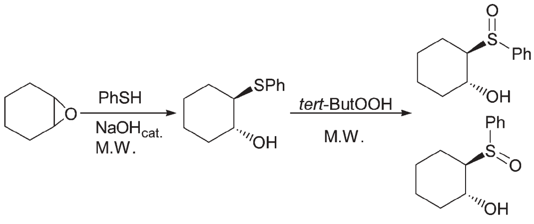

### Microwave-promoted synthesis of β-hydroxy sulfides and β-hydroxy sulfoxides in water

Vincenza Pironti* and Stefano Colonna

Water has many attractions: it is an environmentally benign solvent and a valid alternative to toxic or damaging volatile organic solvents. The use of microwave irradiation in this medium affords the reaction products in high yields, in very short times in the absence of catalysts and without need for further purification while minimizing chemical waste.

## AUTHOR INDEX

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# Green Chemistry 2005: new look, new people, new chances

DOI: 10.1039/b418779m

With the publication of this first issue of *Green Chemistry* in 2005, we would like to give you a brief update on the development of the journal in the past year and on some important changes that have been introduced with the beginning of this year.

## Journal changes

Readers will have noticed that the journal has a striking new look for 2005. The new modern cover design and size makes *Green Chemistry* immediately recognizable as part of the successful RSC journal family. Individual issues will now feature artwork from the most significant paper/review within the issue at the invitation of the Editor thus enhancing the impact of the journal.

A news publication *Chemical Technology* forms part of the introductory pages of *Green Chemistry*. This publication draws together news and research highlights from a variety of RSC publications and provides a snapshot of developments across the chemical technology sector. The introduction of *Chemical Technology* also allows the inclusion of full colour contents lists with graphical abstracts making it easier for you to browse for your favourite article when *Green Chemistry* arrives on your desk. To enhance readability and impact further the font size in the journal has also been increased.

Furthermore, you will notice that "G" pages have disappeared from the journal in order to achieve greater consistency with other RSC journals. The news material will, however, remain an important part of the journal and we encourage the submission of essays, conference reports and other relevant information to the News Editor.

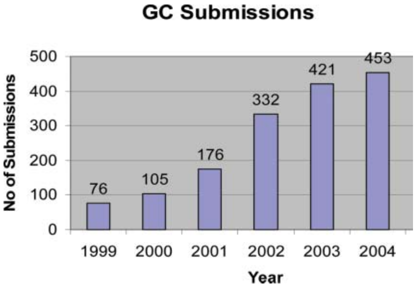
## Editorial Board changes

With the turn of the year, the Editorial Board has also seen considerable changes owing to the fact that a number of members have completed their term at the end of 2004. Throughout the year, there are still other changes in the pipeline as current members complete their three year terms and we will announce these at the appropriate time.

At this stage, we say farewell to Professor Tony Barrett, Professor Terry Collins, Dr Leo Petrus, and Dr Adisa Azapagic with heartfelt thanks for their excellent commitment and support for the journal over the last three years. Their efforts have been pivotal in the success story of *Green Chemistry*!

At the same time, we welcome our new Editorial Board Members in 2005. We are happy and proud to announce that Professor C. J. Li (see photo and biography in issue 2) has joined the Board as our new North American Editor for *Green Chemistry*. Together with Professor Paul Anastas, Professor Roshan Jachuk and Professor Tom Welton, the new team is lined up nicely to shape a bright future for the journal.

## Submissions, publication times, and impact



The ever increasing numbers of papers submitted to the journal continue to reflect the growing interest in *Green Chemistry* as a subject and journal. Our publication times remain amongst the fastest in the field, with average receipt to publication times of around 100 days, ensuring your research is given the highest priority. At the same time, *Green Chemistry* is now more conscious than ever that it has to maintain the highest possible scientific standards. As a consequence, the acceptance rate was consistently around 30% throughout 2004. This stringent policy is supported by a rising impact factor reaching 2.82 in 2004.

## Supporting our authors and referees

The RSC has developed a number of tools to help our authors and referees through the publication process and *Green Chemistry* authors can take full advantage of these developments.

**ReSourCe** provides authors and referees with a single web account for their publishing activities with manuscript tracking and proofing facilities. Authors are also able to access a list of their previous manuscripts and for published articles collect their free PDF reprints and link to the online articles. For further details, please check out http://www.rsc.org/resource.

A recent collaboration with the Unilever Centre for Molecular Science Informatics (at the University of Cambridge, UK) has resulted in the **Experimental Data Checker**—a java applet which analyses experimental data. Again further information is found at the corresponding web page http://www.rsc.org/is/journals/checker/run.htm.

## Thank you

Finally, and most importantly, we would like to express our thanks and gratitude to everyone who has supported *Green Chemistry* by contributing excellent papers, providing valuable and speedy referees' reports, or any other form of collaboration. It has been great fun to work with you over the last year and we look forward to reflecting the continuing growth of the Green Chemistry Community and its scientific achievements in the years to come.

*We wish you all a peaceful turn of the year and every success in 2005!*

*Walter Leitner*
Scientific Editor

*Harp Minhas*
Managing Editor

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# Biodegradable ionic liquids Part II. Effect of the anion and toxicology†

M. Teresa Garcia,*[a] Nicholas Gathergood‡[b] and Peter J. Scammells*[b]

*Received 3rd August 2004, Accepted 18th November 2004*
*First published as an Advance Article on the web 13th December 2004*
**DOI: 10.1039/b411922c**

Although ionic liquids are generally referred to in a 'green' context, little is known about their degradation in the environment. Part I of this series focused on the biodegradability of the commonly used dialkylimidazolium ionic liquids and the effect of the imidazolium cation on biodegradability. We now report the influence of the anion on biodegradability. Preliminary investigations into the toxicology of ionic liquids are also described.

## Introduction

Although there has been intense interest in the use of ionic liquids (ILs) as green solvents,[1] relatively little is known about their biodegradability and toxicity, basic properties in the environmental risk assessment of any organic compound. We recently conducted the first study of IL biodegradability[2] and other groups have begun looking at their toxicology.[3] In Part I of this series, we reported that the commonly used dialkylimidazolium ILs (bmimX) showed negligible biodegradability in the Closed Bottle Test (OECD 301D). The incorporation of an ester in the side chain of the imidazolium cation significantly increased biodegradability. 3-Methyl-1-(pentoxycarbonylmethyl)imidazolium bromide (**1**) proved to be the most biodegradable compound in this series (32% degradation after 28 days). It is postulated that this improved biodegradation is due to an enzymatic hydrolysis step which initiates a pathway to further breakdown products. Consistent with this suggestion, the corresponding amide analogs (compound **2**)

**Nicholas Gathergood**

*Dr Nicholas Gathergood completed his PhD at Southampton University with Prof. Richard Whitby in 1998. His first post-doctorial position was with Prof. Karl Anker Jørgensen at Aarhus University, Denmark. Dr Gathergood joined Prof. Scammells group in 2001, working initially at Deakin University, then at the Victorian College of Pharmacy, Monash University. In November 2004 Dr Gathergood was appointed as lecturer in organic chemistry at Dublin City University. His research interests include medicinal chemistry, asymmetric catalysis, chiral macrocycles and potential applications for ionic liquids.*

**Teresa Garcia**

*Dr M. Teresa Garcia received her Ph.D. in chemistry from the University of Barcelona, Spain in 1990. She is currently a research associate in the Surfactant Technology Department of the Chemical and Environmental Research Institute of Barcelona (IIQAB) belonging to the Spanish National Research Council (CSIC). Her research interests include environmental chemistry and ecotoxicology of surfactants.*

**Peter Scammells**

*Prof. Peter Scammells completed his PhD at Griffith University under the supervision of Prof. Ron Quinn in 1991. After research appointments at the University of South Florida and the Technische Universität Darmstadt, he took up a lectureship at Deakin University in 1993. Prof. Scammells is currently Head of the Department of Medicinal Chemistry and Professor of Medicinal Chemistry at the Victorian College of Pharmacy, Monash University. His research interests include the medicinal chemistry of adenosine and opiate receptors and potential applications for ionic liquids in pharmaceutical synthesis.*

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† For Part I see ref. 2*b*
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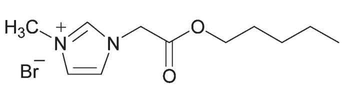
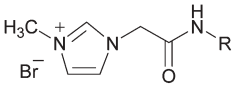
*mtgbet@iiqab.csic.es (M. Teresa Garcia)
peter.scammells@vcp.monash.edu.au (Peter J. Scammells)

were poorly biodegradable. In this paper we examine the effect of the anion on a series of ILs containing an ester group in the side chain and compare these to BmimBr examples. Levels of biodegradation are usually dependent on compound stability and toxicity. To determine which of these factors is dominant a toxicology study of a series of ionic liquids was also performed. The effect of both the counter-ion and the alkyl chain length on the aquatic toxicity of alkylmethylimidazolium ionic liquids was investigated. For this purpose, two short-term bioassays, luminescent bacteria and *Daphnia magna* tests, were applied. These bioassays show good sensitivity and have been used to evaluate the toxicity of many classes of chemical contaminants.[4]



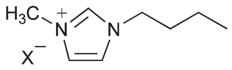
**1**



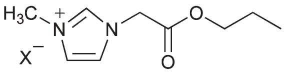
**2**

## Results and discussion

Two types of ILs were initially prepared. The 1-butyl-3-methylimidazolium series (compounds **3a–f**) were prepared using straightforward literature methodology.[5] The 1-(propoxycarbonyl)methyl-3-methylimidazole series were prepared using the synthetic approach described in Part I of this series.[2b] Briefly, this involved the alkylation of methyl imidazole with propyl bromoacetate followed by metathesis to introduce the counter-ion of choice.



**3a** X = Br
**3b** X = $BF_4$
**3c** X = $PF_6$
**3d** X = $NTf_2$
**3e** X = $N(CN)_2$
**3f** X = $C_8H_{17}OSO_3$



**4a** X = Br
**4b** X = $BF_4$
**4c** X = $PF_6$
**4d** X = $NTf_2$
**4e** X = $N(CN)_2$
**4f** X = $C_8H_{17}OSO_3$

### Ultimate biodegradability

The ILs prepared in this study were evaluated using the 'Closed Bottle Test' (OECD 301D).[6] In this test the IL was added to an aerobic aqueous medium inoculated with wastewater microorganisms and the depletion of dissolved molecular oxygen was measured for a defined period of time and reported as a percentage of the theoretical maximum. Duplicate bottles of each series were analysed at the start of the test for dissolved oxygen and the remaining bottles were incubated at 20 °C $\pm$ 1 °C in the dark. Bottles of all series were withdrawn in duplicate for dissolved oxygen analysis over the 28 day incubation period. A control with inoculum, but without test chemicals was run in parallel for the determination of oxygen blanks. Sodium *n*-dodecyl sulfate (SDS) was used as reference substance. Compounds which reached a biodegradation level higher than 60% are referred to as "readily biodegradable". The results obtained for the butylmethylimidazolium cation with a range of anions are shown in Fig. 1.

1-Butyl-3-methylimidazolium octylsulfate underwent a modest amount of biodegradation (25%) after 28 days, while the other ILs remained largely intact (less than 5% biodegradation).

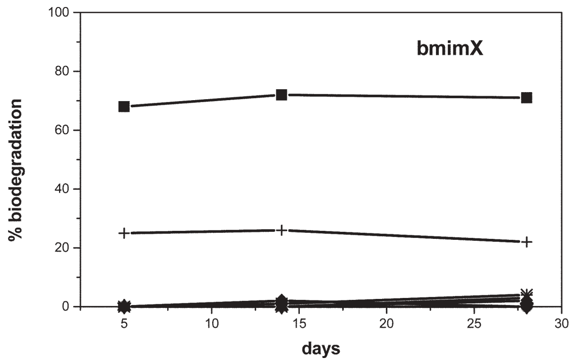


**Fig. 1** Biodegradation curves of the butylmethylimidazolium salts with different counter-ion: bmimBr (●), bmimCl (▲), bmimBF$_4$ (▼), bmimPF$_6$ (♦), bmimoctyl-OSO$_3$ (+), bmimN(CN)$_2$ (×), bmimNTf$_2$(*); reference substance: SDS (■).

Clearly none of the ILs tested were "readily biodegradable". The higher percentage of biodegradation observed for the octyl sulfate anion is not surprising as linear alkyl sulfates are well known to be readily biodegradable.[7] BOD/COD for sodium dodecyl sulfate was more than 60% within 5 days incubation in the Closed Bottle Test (Fig. 1) confirming the excellent and very rapid ultimate biodegradation of linear alkyl sulfates even in this relatively stringent test system. Initial attack of these molecules is effected by enzymatic cleavage of the sulfate ester bond leaving inorganic sulfate and fatty acid. The further degradation of the fatty alcohol sulfate intermediates, the fatty acids, proceeds *via* β-oxidation enabling the utilization of the organic moiety of the molecule for energy and biomass production.[8]

The 3-methyl-1-(propoxycarbonyl)imidazolium series showed higher biodegradability for all corresponding anions (Fig. 2). This result was consistent with the findings from our earlier study[2] in which the incorporation of a side chain ester moiety increased biodegradation. Once again, the most biodegradable compound in this series possessed the octyl sulfate anion (49% biodegradation after 28 days).

Although modifications of the anion led to changes in the physical and chemical properties of the ionic liquids, the effect of the counter-ion on biodegradability was generally not pronounced. The octyl sulfate anion proved to be an exception, showing significantly higher biodegradability in both test sets.

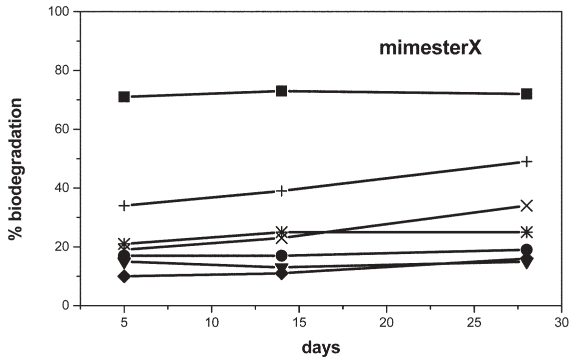


**Fig. 2** Biodegradation curves of the 3-methyl-1-(propyloxycarbonyl)-imidazolium X; X = Br (●), BF$_4$ (▼), PF$_6$ (♦), octyl-OSO$_3$ (+), N(CN)$_2$ (×), NTf$_2$ (*); reference substance: SDS (■).

The introduction of an organic anion readily catabolised clearly improved the extent of ultimate biodegradation.

The ionic liquid containing an ester moiety in the side chain of the imidazolium cation and the octyl sulfate anion (compound **4f**) reached the highest extent of biodegradation. The incorporation of chemical bonds susceptible to enzymatic hydrolysis, resulted in a significant enhancement of biodegradability compared with commonly used dialkylimidazolium ionic liquids bmimBF$_4$ and bmimPF$_6$.

## Toxicity assessment

Acute toxicity tests on freshwater crustacea (*Daphnia magna*)[9] as well as on saltwater bacteria (*Photobacterium phosphoreum*)[10] were carried out to assess the aquatic toxicity. The results of both *Daphnia magna* 24 h immobilisation test (IC$_{50}$) and *Photobacterium phosphoreum* 30 min luminescence reduction test (EC$_{50}$) for the 1-alkyl-3-methylimidazolium cation with different anions are given in Table 1.

The estimated concentration able to immobilise 50% of the crustacea population (IC$_{50}$) ranged from 4 to 90 μmol L$^{-1}$ (from 0.54 to 1.85 in logarithmic form) whereas the effective concentration resulting in a 50% reduction of light produced by the bacteria (EC$_{50}$) ranged from 10 to 2200 μmol L$^{-1}$ (from 0.95 to 3.34 in logarithmic form).

These data indicate that the *Daphnia magna* are much more sensitive to the toxic effects of 1-butyl-3-methylimidazolium salts than bacteria (*i.e.* the IC$_{50}$ values are an order of magnitude less than EC$_{50}$ values). Differences in toxicity of 1-alkyl-3-methylimidazolium ILs become less pronounced with increasing alkyl chain length.

The toxicity data were compared with corresponding data for commonly used organic solvents (Table 2) and other quaternary ammonium compounds (Table 3).

For *Daphnia magna*, the 1-alkyl-3-methylimidazolium ionic liquids generally proved to be much more toxic than the non-chlorinated organic solvents (as evidenced by differences in IC$_{50}$ values of more than three orders of magnitude). These ILs also proved to be more toxic than the chlorinated solvents, dichloromethane and chloroform, though the difference was less pronounced (30–45 and 2–3 times more toxic, respectively). Likewise, imidazolium salts are clearly more toxic than organic solvents against *Photobacterium phosphoreum*, although the differences in the effective concentrations are lower than for crustacea.

**Table 1** Acute toxicity of 1-alkyl-3-methylimidazolium ionic liquids on *Daphnia magna* and *Photobacterium phosphoreum*

| | *D. magna*, IC$_{50}$/μmol L$^{-1}$ log IC$_{50}$, 95% CI | *P. phosphoreum*, EC$_{50}$/μmol L$^{-1}$ log EC$_{50}$, 95% CI |
|---|---|---|
| bmimBr | 1.78 ± 0.07 | 3.27 ± 0.09 |
| bmimCl | 1.85 ± 0.06 | 3.34 ± 0.13 |
| bmimBF$_4$ | 1.79 ± 0.05 | 3.10 ± 0.17 |
| bmimPF$_6$ | 1.95 ± 0.03 | 3.07 ± 0.29 |
| hmimCl | 1.09 ± 0.05 | 2.32 ± 0.16 |
| hmimBF$_4$ | 1.13 ± 0.05 | — |
| hmimPF$_6$ | — | 2.17 ± 0.06 |
| omimCl | 0.54 ± 0.07 | 1.19 ± 0.11 |
| omimBF$_4$ | 0.66 ± 0.07 | — |
| omimPF$_6$ | — | 0.95 ± 0.12 |

**Table 2** Acute toxicity of organic solvents on *Daphnia magna* and *Photobacterium phosphoreum*

| Organic solvent | *D. magna*, IC$_{50}$/μmol L$^{-1}$ log IC$_{50}$[a] | *P. phosphoreum*, EC$_{50}$/μmol L$^{-1}$ log EC$_{50}$[b] |
|---|---|---|
| Methanol | 5.85 | 6.51 |
| Ethanol | 5.33 | 5.89 |
| Isopropanol | 5.22 | 5.72 |
| Acetonitrile | 5.39 | 5.57 |
| Acetone | 5.37 | 5.17 |
| Dichloromethane | 3.42 | 4.57 |
| Chloroform | 2.24 | 4.16 |

[a] *D. magna* data taken from Kaiser.[11a] [b] *P. phosphoreum* data taken from Kahru.[11b]

**Table 3** Acute toxicity of quaternary ammonium surfactants on *Daphnia magna* and *Photobacterium phosphoreum*

| Surfactant[a] | *D. magna*, IC$_{50}$/μmol L$^{-1}$ log IC$_{50}$ | *P. phosphoreum.* EC$_{50}$/μmol L$^{-1}$ log EC$_{50}$ |
|---|---|---|
| DT | 0.09[b] | −0.11[b] |
| TT | −0.38[b] | −0.08[b] |
| HT | −0.45[b] | 0.24[b] |
| DBD | −0.47[b] | −0.33[b] |
| Im-1 | — | −0.41[c] |
| Im-2 | — | −0.23[c] |
| Bis-Im | — | −0.18[c] |

[a] DT, dodecyl trimethyl ammonium bromide; TT, tetradecyl trimethyl ammonium bromide; HT, hexadecyl trimethyl ammonium bromide; DBD dodecyl benzyl dimethyl ammonium bromide; Im-1, 1-decyl-3-hexyloxymethylimidazolium chloride; Im-2, 1-decyl-3cyclohexyloxymethyl imidazolium chloride; Bis-Im, 3,3′-(2,7-dioxyoctylmethylene)bis(1-octyl imidazolium) chloride. [b] Data reported by Garcia *et al.*.[12a] [c] Data reported by Nalecz-Jawecki *et al.*.[12b]

The structural similarity between dialkylimidazolium ionic liquids and cationic surfactants possessing an imidazolium core prompted us to compare their aquatic toxicity values. In both bioassays, cationic surfactants were more toxic than dialkyimidazolium ionic liquids. In the *Daphnia magna* test, cationic surfactants have effective concentrations between 50 and 300 times lower than the butylmethylimidazolium ionic liquids investigated. In luminescent bacteria, differences in EC$_{50}$ values are of three orders of magnitude. As the alkyl chain length of the ionic liquids increases, toxicity differences with the cationic surfactants decrease significantly.

Bearing in mind that biological membranes are essentially non-polar interfaces, evidence exists that the toxicity of chemicals against the aquatic species is caused by the ability of the molecules to disrupt the integral membrane by a hydrophobic/ionic adsorption phenomenon at the cell membrane–water interface. Hydrophobic molecules have a greater ability to accumulate at this interface. Therefore, higher toxicity would be expected with increasing hydrophobicity in the molecule, as reported for anionic surfactants on *Daphnia magna*[13] and for alcohol ethoxylated surfactants on *Photobacterium phosphoreum*.[14] Accordingly, the aquatic toxicity increased with the alkyl chain length for the 1-alkyl-3-methylimidazolium ionic liquids investigated and linear relationships between both parameters were established

(Fig. 3). This finding is in keeping with other recently reported investigations into IL toxicity.[3]

The quantitative structure–activity relationships obtained between toxicity and alkyl chain length provides evidence that the potency of the biological activity is closely related to structural parameters that determine the hydrophobicity of the molecule and hence, its organism–water partitioning properties. On the contrary, our results suggest that the nature of the inorganic anion has only a little effect.

## Conclusions

Series of butylmethylimidazolium [bmimX, X = Br, $BF_4$, $PF_6$, $NTf_2$, $N(CN)_2$ and $octylOSO_3$] and methyl (propoxycarbonyl)-imidazolium ionic liquids were prepared and evaluated using the Closed Bottle Test (OECD 301 D). The bmim series generally proved to be poorly biodegradable, with all but one member of this series showed little or no degradation after 28 days. The corresponding 3-methyl-1-(propoxymethylcarbonyl)-imidazolium series showed higher levels of biodegradability. However, none of the compounds that were tested could be classified as "readily biodegradable". In both series ILs with the octyl sulfate anion conferred higher levels of biodegradability.

Two short term bioassays were used to evaluate IL toxicity—the *Daphnia magna* immobilisation test and the *Photobacterium phosphoreum* luminescence reduction test. The dialkylimidazolium ILs that were analysed proved to be more toxic than conventional organic solvents in both bioassays.

## Experimental

### Synthesis

1-*n*-Butyl-3-methylimidazolium ionic liquids (**3**) [bmimX, where X = Cl, Br, $BF_4$, $PF_6$, $NTf_2$, $N(CN)_2$ and $octylOSO_3$] were prepared according to literature methods.[5] 1-*n*-Hexyl-3-methylimidazolium and 1-*n*-octyl-3-methylimidazolium ionic liquids (X = Cl, $BF_4$ and $PF_6$) were also prepared using literature methods.[2b]

The syntheses of 3-methyl-1-(propyloxycarbonyl)imidazolium ionic liquids (**4a–f**) were as reported in Part I of this series[2] or as described below.

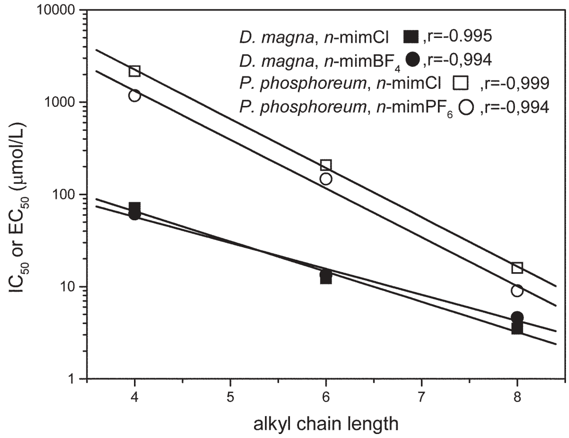


**Fig. 3** Effect of the alkyl chain length on the acute toxicity for 1-alkyl-3-methylimidazolium ionic liquids.

Sodium dicyanamide (96%) and octyl sulfate, sodium salt (95%) were purchased from Aldrich. All organic solvents were dried and distilled before use. ILs were washed with distilled water.

All NMR spectra of ILs were recorded in $CD_3CN$ (Aldrich 15,180-7, 99.8 atom%D) on a Bruker Avance DPX 300 spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded at 300 MHz and 75.4 MHz, respectively.

### 1-*n*-Butyl-3-methylimidazolium bromide dicyanamide (3e)

The title compound was prepared analogously to (**4e**) using 1-*n*-butyl-3-methylimidazolium bromide (**3a**) (3.00 g, 13.7 mmol) and $NaN(CN)_2$ (1.46 g, 16.4 mmol) to give a clear oil in 78% yield (2.19 g, 10.7 mmol). $^1H$ NMR (300 MHz, $CD_3CN$) $\delta$ 9.20 (s, 1H), 7.50 (s, 1H), 7.46 (s, 1H), 4.20 (t, $J$ = 7.0 Hz, 2H), 3.89 (s, 3H), 1.82 (tt, $J$ = 7.5, 7.5 Hz, 2H), 1.30 (tt, $J$ = 7.5, 7.5 Hz, 3H), 0.92 (t, $J$ = 7.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ 137.55, 124.54, 123.23, 50.14, 36.84, 32.62, 19.94, 13.68. Peaks for $N(CN)_2^-$ not cited.

### 1-*n*-Butyl-3-methylimidazolium octylsulfate (3f)

The title compound was prepared according to a literature procedure using 1-butyl-3-methylimidazolium bromide (**3a**) (3.02 g, 14 mmol) and $Na(n–C_8H_{17}O–SO_3)$ (2.70 g, 11.6 mmol) in distilled water (5 mL) in 72% yield (2.92 g, 8.4 mmol).[5d] $^1H$ NMR (300 MHz, $CD_3CN$) $\delta$ 8.89 (s, 1H), 7.45 (s, 1H), 7.41 (s, 1H), 4.16 (t, $J$ = 7.0 Hz, 2H), 3.86 (s, 3H), 3.82 (t, $J$ = 7.0 Hz, 2H), 1.82 (tt, $J$ = 7.5, 7.5 Hz, 2H), 1.56 (tt, $J$ = 7.5, 7.5 Hz, 2H), 1.34 (tt, $J$ = 7.5, 7.5 Hz, 2H), 1.35–1.24 (m, 10H), 0.93 (t, $J$ = 7.0 Hz, 3H), 0.87 (t, $J$ = 7.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ 137.82, 124.69, 123.35, 67.38, 50.27, 36.85, 32.73, 32.65, 30.52, 30.16, 30.08, 26.90, 23.44, 20.07, 14.47, 13.78.

### 3-Methyl-1-(propoxycarbonylmethyl))imidazolium $N(CN)_2$ (4e)

A dry flask was charged with 3-methyl-1-(propoxycarbonyl)-imidazolium bromide (**4a**) (2.10 g, 7.7 mmol) and dry acetonitrile (5 mL) under a nitrogen atmosphere. $NaN(CN)_2$ (821 mg, 9.3 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at rt. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (2 × 1 mL). The filtrate and washings were combined, solvent removed by rotary evaporation then *in vacuo*. The product was dried at 60 °C at 0.01 mmHg for 72 h to give a clear viscous oil in 93% yield (1.79 g, 7.2 mmol). $^1H$ NMR (300 MHz, $CD_3CN$) $\delta$ 9.16 (s, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 5.23 (s, 2H), 4.15 (t, $J$ = 7.0 Hz, 2H), 3.91 (s, 3H), 1.67 (tt, $J$ = 7.0, 7.0 Hz, 2H), 0.94 (t, $J$ = 7.0 Hz, 3H). $^{13}C$ NMR (75 MHz, $CD_3CN$) $\delta$ 167.89, 139.01, 125.06, 124.70, 69.10, 51.27, 37.56, 22.94, 10.90. Peaks for $NCNCN^-$ not cited. MS (ESI): *m*/*z*, 183.1 $[M–NCNCN^-]^+$; MS (ESI): *m*/*z*, 66 $[N(CN)_2^-]$.

### 3-Methyl-1-(propoxycarbonylmethyl))imidazolium octylsulfate (4f)

The title compound was prepared according to a literature procedure using 3-methyl-1-(propoxycarbonyl)imidazolium bromide (**4a**, 1.40 g, 5.3 mmol) and $Na(n–C_8H_{17}O–SO_3)$

(1.04 g, 4.5 mmol) in distilled water (2 mL) in 58% yield (1.02 g, 2.6 mmol).[5d] $^1$H NMR (300 MHz, $CD_3CN$) $\delta$ 8.74 (s, 1H), 7.44 (s, 1H), 7.40 (s, 1H), 5.05 (s, 2H), 4.16 (t, $J$ = 7.0 Hz, 2H), 3.89 (s, 3H), 3.80 (t, $J$ = 7.0 Hz, 2H), 1.68 (tt, $J$ = 7.5, 7.5 Hz, 2H), 1.65–1.52 (m, 2H), 1.40–1.20 (m, 10H), 0.95 (t, $J$ = 7.0 Hz, 3H), 0.89 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (75 MHz, $CD_3CN$) $\delta$ 168.16, 139.48, 125.76, 124.61, 68.72, 67.97, 50.80, 37.19, 32.84, 30.34, 30.25, 26.97, 23.61, 22.80, 14.80, 10.95. MS (ESI): *m*/*z*, 183.1 $[M–C_8H_{17}OSO_3^-]^+$; MS (ESI): *m*/*z*, 209.1 $[C_8H_{17}OSO_3^-]$.

### Closed bottle test[6]

The biodegradability of the test compounds was evaluated using the "Closed Bottle Test" (OECD 301 D). In this method, the chemical being evaluated is added to an aerobic aqueous medium inoculated with wastewater microorganisms and the depletion of dissolved molecular oxygen is measured for a defined period of time and reported as a percentage of the theoretical maximum. Compounds which reach a biodegradation level higher than 60% are referred to as "readily biodegradable".

Sodium *n*-dodecyl sulfate (SDS) was used as reference substance. Solutions containing 2 mg $L^{-1}$ of the test ionic liquids and the reference chemical as sole sources of organic carbon were prepared, separately, in previously aerated mineral medium. The solutions were then inoculated with secondary effluent collected from an activated sludge treatment plant and each well-mixed solution was carefully dispensed into a series of BOD bottles so that all the bottles were completely full. A control with inoculum, but without test chemicals was run parallel for the determination of oxygen blanks. Duplicate bottles of each series were analysed immediately for dissolved oxygen and the remaining bottles were incubated at 20 °C ± 1 °C in the dark. Bottles of all series were withdrawn in duplicate for dissolved oxygen analysis over the 28-day incubation period. The biodegradation after *n* days was expressed as the ratio of the biochemical oxygen demand (BOD) to the chemical oxygen demand (COD) both of them expressed as mg $O_2$ per mg compound. The chemical oxygen demand was determined by the dichromate reflux method.[15] For the calculation of the biochemical oxygen demand the determined oxygen depletions were divided by the concentration of ionic liquid.

### *Daphnia magna* immobilisation test

*Daphnia magna*, laboratory bred, not more than 24 hours old were used in this test, where swimming incapability is the end point. The pH of the medium was 8.0 and the total hardness was 250 mg $L^{-1}$ (as $CaCO_3$), with a Ca : Mg ratio of 4 : 1. Tests were performed in the dark at 20 °C. Twenty Daphnia, divided into four groups of five animals each, were used at each test concentration. For each surfactant, ten concentrations in a geometric series were tested in the concentration range first established in a preliminary test. The percentage immobility at 24 hours was plotted against concentration on logarithmic-probability paper, a linear relationship was obtained and the $IC_{50}$ was calculated from the corresponding equation.

### *Photobacterium phosphoreum* luminescence reduction test (Microtox test)[10]

*Photobacterium phosphoreum* is a marine luminescent bacterium naturally adapted to a saline environment. These bacteria liberate energy in the form of visible light (intensity maximum at 490 nm) as a consequence of a series of metabolic reactions. On exposure to toxic substances, the light output is reduced and this reduction is proportional to the toxicity of the sample. Therefore, the toxicity bioassay is based on the light emission of these bacteria, as a measurement of their metabolic activity. In the Microtox bioassay the concentration of an aqueous solution of a chemical that causes a 50% reduction of the light emitted by the bacteria ($EC_{50}$) is calculated from a concentration-response curve by regression analysis. The osmotic pressure of the samples was adjusted by NaCl addition (2%). Toxicity data were based on a 30 min exposure of bacteria to the surfactant solution at 15 °C.

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# Industrial application of ionic liquids as performance additives†

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*Received 23rd July 2004, Accepted 24th September 2004*
*First published as an Advance Article on the web 25th November 2004*
**DOI: 10.1039/b411357h**

Over the last decade ionic liquids have achieved much attention and are not any longer just a class of esoteric compounds, but are proving to be valuable and useful in a multitude of different applications. So far, ionic liquids have mainly been considered to be an alternative to conventional solvents in reaction and separation processes. Hence, it is not surprising that most of the recent publications report on the use of ionic liquids as a solvent for chemical and biochemical syntheses. This may be rationalized by the possibility of carrying out biphasic reactions for the separation and recovery of otherwise homogenous precious metal catalysts or enzymes, as ionic liquids form two phases with many organic product mixtures. In contrast, the use of ionic liquids as performance additives or as reactive component in the preparation of oligomers or pre-polymers has gained far less attention. The authors believe that due to their unique properties ionic liquids have a great potential to be used as performance additives in many materials and applications. The application of ionic liquids is in accordance with the chemical industry's guidelines and principles concerning the initiatives ''sustainable development'' and ''responsible care''. The authors demonstrate this by provision of an example taken from Degussa's ongoing ionic liquids research program: The use of ionic liquids as secondary dispersant in universal pigment pastes, *i.e.* in the white base paint to be tinted.

## Introduction

Recently, ionic liquids have been extensively evaluated as environmentally friendly or ''green'' alternatives[1] to conventional organic solvents for a broad range of organic synthetic applications.[2] In addition, ionic liquids have been used *e.g.* as catalysts[3] in organic synthesis, in compositions for stabilizing and/or isolating nucleic acids in or from micro-organisms,[4] as process aids for the synthesis of polynucleotides,[5] as lubricants[6] and for the preparation and stabilization of nanoparticles.[7] Furthermore, after the announcement of the first industrial process involving ionic liquids by BASF (BASIL[8] process) in 2003 the potential of ionic liquids for new chemical processes and technologies is beginning to be recognized.

## Ionic liquids as performance additives

### Unconventional ionic liquids

So far, academic and industrial research have paid very little attention to the use of ionic liquids as performance additives or as reactive component in the preparation of oligomers or

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† This work was presented at the Green Solvents for Synthesis Meeting, held in Bruchsal, Germany, 3–6 October 2004.
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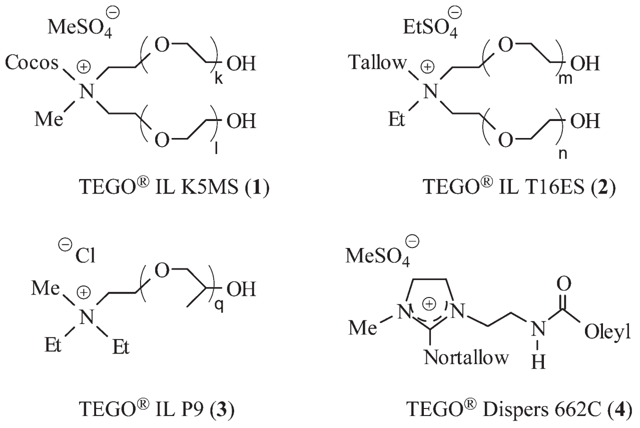
**Kathrin Lehmann**

pre-polymers.[9] Only very few publications, mainly from academic sources, can be found in the literature reporting on the use of ionic liquids as *e.g.* plasticizers for polymers such as polyamides,[10] PVC[11] and PMMA.[12] Some patent applications teach the use of ionic liquids in surface and air treating compositions for household and automobile applications,[13] in ink composition[14] and as an antistatic agent.[15] A reason for this might be the high price of imidazolium-based ionic liquids compared to those prices of other solvents or additives. Another drawback of imidazolium-based ionic liquids is their listing status. Most of the imidazolium-based ionic liquids are not listed in EINECS (European Inventory of Existing Commercial Substances) or TSCA (Toxic Substances Control Act) which means that in order to be legally allowed to produce and use them in technical quantities they have to be toxilogically evaluated and registered. This would not only consume a significant amount of time but also financial resources depending on the quanitity to be dealt with, and the outcome would be an uncertain one. On the other hand, a whole range of already listed and toxicologically evaluated ionic liquids exists, but surprisingly has not achieved much attention until today. Therefore, we would like to draw the ionic liquids community's attention to these non-imidazolium-based ionic liquids which are readily available in technical quantities for reasonable prices and hence, represent an interesting alternative to the much more expensive and often not yet listed imidazolium-based ionic liquids. For the purpose (context) of this article we would like to refer to imidazolium-based ionic liquids as *conventional* and to non-imidazolium-based ionic liquids as *unconventional* ionic liquids. Many acyclic ammonium salts and quaternized heterocyclic compounds such as imidazolinium or oxazolinium salts satisfy the well accepted definition for ionic liquids which is a melting point below 100 °C or even below room temperature (RTILs). Thus, these salts can be regarded as unconventional ionic liquids. Whereas great attention has been paid to conventional ionic liquids, less research effort has focused on unconventional ionic liquids.[16] Some of the unconventional ionic liquids we evaluated towards their use as performance additives during the course of our investigations are depicted in Fig. 1.

We believe that due to their unique properties ionic liquids and particularly unconventional ionic liquids have a great potential to be used in the sense of a performance additive. Unconventional ionic liquids are readily available and should find use not only as plasticizers for plastics, but also as additives in the area of coatings, lacquers and inks. Herein, we report on the first industrial application of ionic liquids as performance additives. Ionic liquids were incorporated either as secondary dispersant in universal pigment pastes or in the white base paints to be tinted.



TEGO® IL K5MS (**1**) TEGO® IL T16ES (**2**)

TEGO® IL P9 (**3**) TEGO® Dispers 662C (**4**)

**Fig. 1** Commercially available unconventional ionic liquids.

### Dispersants

It is common practice to use dispersing agents in order to homogeneously stabilize fillers and pigments in liquid media and to obtain storage stable pigment pastes, paints and lacquers. According to the state of the art, dispersing agents have to fulfill the following requirements:

- Easy incorporation of fillers and pigments leading to shorter dispersing times, respectively allowing for the use of simpler and cheaper dispersing aggregates (dissolver instead of ball mills).
- Reduction of the pigment paste viscosity allowing for high pigment loading and economical tinting systems.
- Development of optimal color strength, *i.e.* of the optimal hiding power when using opaque pigments.
- Avoidance of sedimentation in pigment pastes when stored over long periods of time or under extreme climatic conditions.
- Avoidance of flocculation for good reproducability of colors which is becoming particularly important when using mixing machines for the tinting of white base paints and lacquers.

The above listed requirements have to be independently fulfilled regardless of the liquid medium into which a filler or a pigment has to be dispersed. Hence, there has been no lack of attempts to develop polymeric dispersants[17] with a truely universal applicability. Additionally, a good dispersant wets and stabilizes not only inorganic but also organic pigments exhibiting both hydrophilic and hydrophobic surfaces. Most modern polymeric dispersants are universal concerning the pigments but not with respect to the surrounding medium. Generally, a pigment in a solvent-based liquid medium (hydrophobic) is only sterically stabilized whereas a pigment in a water-based medium (hydrophilic) can be both sterically and electronically stabilized depending on the presence of appropriate functional groups in the polymeric dispersant (electro-steric stabilization). Naturally, steric stabilization is only possible when the pigment stabilizing functionalities, *i.e.* parts of a dispersant (*e.g.* side chains in comb-like structures or certain blocks in linear block co-polymeric dispersants) are fully compatible with the surrounding medium. Obviously, the broad range of technical requirements and the diversity of pigments and surrounding media make it extremely difficult to realize a truely universal dispersing agent.

## Results and discussion

Accordingly, it is state of the art to have on the one hand dispersants which are optimized for water-based and on the other hand those dispersants that are designed for solvent-based coatings resulting in different tinting paste systems. The handling of different tinting systems in mixing machines requires a lot of time, money and cleaning operations for the manufacture of such pigment pastes. Moreover, the users of those pastes, *e.g.* building centers and do-it-yourself stores, need space for several tinting machines, as for each tinting, the mixing machine will handle only one specific type of pigment paste. Apparently, there is a high potential of saving costs and logistic efforts if truely universal dispersants were available to the market allowing for the stabilization of any pigment in water-based pastes and then using these water-based pastes for water- *and* solvent-based coatings. Without doubt there have been numerous efforts to develop so-called universal dispersants for the decorative industry during the past few years. Typical structures discussed in that context are alkyl phenol ethoxylates (APE),[18] oleo block ABC derivatives[19] or styrene oxide based polyether structures.[20] However, in Europe the use of APEs is restricted in a variety of applications and will have to be completely ceased in the near future in the coating industry. The degradation process of APEs leads to phenolic species (intermediates) with high fish toxicity.[21] Furthermore, it is assumed that APEs interfere with the human hormone cycle as endocrine disrupters. Recently, Degussa has developed a novel class of unique styrene oxide-based phosphorylated polyethers[20] (illustrated in Fig. 2) and their corresponding anionic species as an environmental-friendly and promising alternative to alkyl phenol ethoxylates.

These novel primary dispersants will expand the prevelance of water-based, *i.e.* universal pigment pastes. In doing so this will lead to a reduction of the consumption of VOCs, as improved universal pigment pastes are expected to successively replace solvent-based pigment pastes. Furthermore, since in the course of their degradation such styrene oxide-based phosphorylated polyethers do not lead to any kind of phenolic intermediates, their development can be seen as a contribution to the "responsible care" initiative. However, undoubtedly there is still room for improvement as shown in Table 1. Particularly, in the area of solvent-based coating systems and the search for better pigment pastes, *i.e.* better and more universal dispersants will continue.

It is common practice to use modern water-based universal pigment pastes (also called colorants) to tint every kind of water-based coating or laquer, *e.g.* flat and high gloss acrylics, PVAc-based paints or alkyd emulsion-based systems, as well as typical solvent-based coating systems such as air-drying enamels based on conventional alkyds solubilized in white spirit or solvent-based polyurethane modified alkyds. However, using the same universal colorant in special solvent-based systems, *e.g.* high solid isoparaffin-based alkyds or so-called Pliolite® systems does not yield the desired result (see the "×" in Table 1). The phenomenon is illustrated in Fig. 3: A red, a purple and a blue universal colorant were used to tint a Pliolite® coating system. A significant color difference is observed when comparing the left top quadrants (I) of the draw downs with the left bottom quadrants (II). This difference is referred to as rub-out value Δ*E*.‡ Therefore, one could question the general validity of the term "universal" pigment paste.

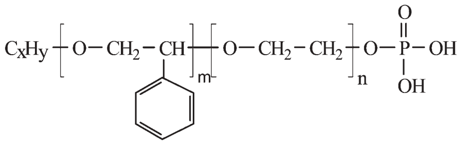


**Fig. 2** Phosphoric acid ester of a styrene oxide-based polyether.

**Table 1** Suitability of different pigment paste systems in several coating systems

| | Coating system | | |
|---|---|---|---|
| Pigment paste | Water-based systems | Typical solvent-based systems | Special solvent-based systems (*e.g.* Pliolite®) |
| Water-based | ✓ | — | — |
| Solvent-based | — | ✓ | ✓ |
| Universal colorant | ✓ | ✓ | × |

Even additional quantities of the universal colorant do not improve the result in terms of reduced brightness values§ (the lower L* the more effective is the colorant) and reduced Δ*E* values (the lower Δ*E* the better the pigment is stabilized against flocculation); see Table 2. The reason behind this is the inability of the dispersant used in the universal colorant to still stabilize the pigment when mixed with the isoparaffin-based alkyd or so-called Pliolite® system. Now, comparison of the right top quadrants (III) of the draw downs with the right bottom quadrants (IV) clearly demonstrates that this problem can be overcome by using unconventional ionic liquids as secondary dispersing agents. In all three cases (red, purple and blue universal colorant) the rub-out value Δ*E* is almost negligable. The use of ionic liquids indisputably enables universal colorants to be applicable in a truely universal way. Moreover, the combination of ionic liquids and ecofriendly universal dispersants does not only allow for previously unknown dimensions of the applicability of universal pigment pastes but also allows *e.g.* building centers and do-it-yourself stores to realize a improved profitability due to a reduced complexity of the required logistics to offer a large variety of differently colored paints and lacquers.

## Experimental

Typically, the tinting of a white base paint is carried out using the following procedure. 20 parts of a white base paint are mixed with (a) 1.0 part of an inorganic pigment paste which contains *e.g.* 60% of iron oxide red (Bayferrox® 120 M) or (b) 0.5 parts of an organic pigment paste, which contains between 20–40% of dioxazine (Cromophtal® Violett GA) or phthalocyanine blue (Heliogenblue® L 7101 F).

Besides water, the pigment and the dispersant pigment pastes usually contain wetting additives, defoamers and preservatives.

After handmixing the colorant should develop the full color strength in the coating. The development of the full color strenght is indicated by a low L* value (brightness) and a low Δ*E* value. The results presented in Table 2 were obtained using a Pliolite® system (special solvent-based coatings particularly used in the South of Europe and in the UK) and universal pigment pastes based on the unique dispersant technology of Degussa (*vide supra*; Tego® Dispers 650 and Tego® Dispers 651).

Without the addition of an ionic liquid to the mixture of the Pliolite® coating system and one of the three colorants the development of the color strength is miserable and poor. We used four different commercially available unconventional ionic liquids and one conventional ionic liquid (dimethylimidazolium methyl sulfate) to evaluate their impact on the

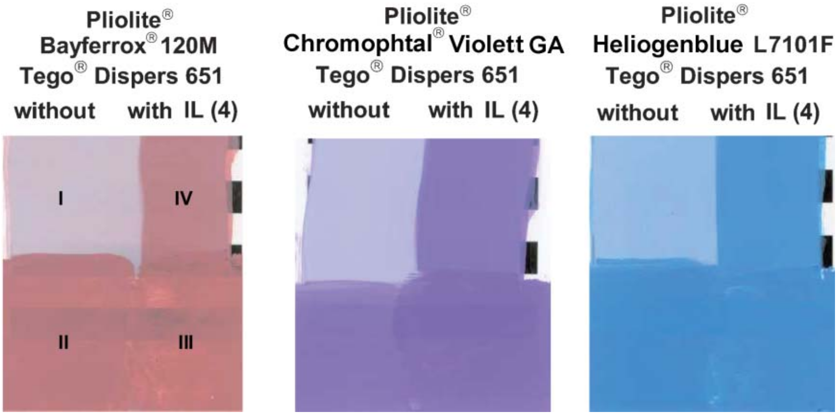


**Fig. 3** Draw downs of Pliolite® tinted with universal colorants based on Tego® Dispers 651 adjusted with ionic liquid Tego® Dispers 662C.

**Table 2** Results obtained by using ionic liquids in mixtures made from Pliolite® and universal colorants

| Ionic liquid | Bayferrox® 120 M | | Cromophtal® Violett GA | |
|---|---|---|---|---|
| | L* | Δ*E* | L* | Δ*E* |
| without IL | 76.15 | 27.67 | 71.16 | 33.73 |
| Tego® IL T16ES | 73.05 | 21.99 | 70.10 | 25.83 |
| Tego® IL K5MS | 72.07 | 21.91 | 68.16 | 24.86 |
| Tego® IL P9 | 64.70 | 12.49 | 69.24 | 29.14 |
| [MMIM][MeSO$_4$][a] | 67.74 | 16.47 | 64.02 | 20.26 |
| Tego® Dispers 662 C | 60.01 | 3.30 | 54.00 | 5.93 |

[a] [MMIM][MeSO$_4$] = 1,3-dimethylimidazolium methylsulfate.

development of the color strength. It turned out that the addition of only 0.4–2% of an ionic liquid to these mixtures significantly improved the color strength. Particularly, when Tego® Dispers 662C was used, the rub-out value Δ*E* came close to zero. The higher the rub-out value Δ*E* the more color pigment has flocculated. Contrary to primary dispersing agents these ionic liquids are secondary dispersing agents. Therefore, they do not have to be used essentially during the grinding of the pigment but can be used at any step during pigment paste manufacture.

Ionic liquids provide the user and the manufacturer of commercial pigment pastes with a higher flexibility regarding the optimization of their products, as ionic liquids can be used according to one of the three following procedures in order to enhance the applicability of universal pigment pastes, respectively to improve the color strength of the final paints, coatings and lacquers:

(A) White base paint + pigment paste based on universal dispersing agent + ionic liquid as third component (so-called post addition),

(B) White base paint already containing an ionic liquid to have the highest flexibility concerning the use of different pastes based on a variety of primary dispersant technologies,

(C) White base paint + pigment paste which contains both the primary dispersant and the ionic liquid to make the colorant universal not only in the old-fashioned way but also in terms of critical solvent-based systems such as Pliolites® or isoparaffin-based alkyds.

It is noteworthy that the efficacy of procedure (A) is higher compared to (C), but requires higher quantities of the ionic liquid.

## Conclusion

The combination of ionic liquids and universal ecofriendly primary dispersants is able to overcome severe problems relating to the use of colorants in problematic solvent-based coatings (*e.g.* Pliolites®). Specifically, unconventional ionic liquids provide a cost-wise attractive solution to the paint and coating industry for the tinting of such problematic solvent-based paints and coatings. Furthermore, the combination of ionic liquids and *state of the art* primary dispersants enables customers of pastes and manufacturers of those to reduce complexity of logistics during storage and manufacture. In summary, we have demonstrated that unconventional ionic liquids can be used in the sense of performance additives, and we believe that due to their unique properties and their broad applicability they will play a major role in the formulation of coating systems in the near future.

## Summary

With this article we would like to change the perception that ionic liquids are mainly (only) environmentally friendly or "green" alternatives to conventional organic solvents. In fact, the application potential of ionic liquids is much broader than presumed. Of course, they can be used as an alternative to conventional organic solvents, but they also can be employed as process aids (*e.g.* in the immobilization[22] of otherwise homogeneous catalysts). Sometimes it is not even necessary to use an ionic liquid in order to improve a chemical process, but one can take advantage of the formation of an ionic liquid during the process (*e.g.* BASIL[8] process). Another possibility to benefit from the unique properties of ionic liquids is their application as performance additives. In this context, non-imidazolium-based (*unconventional*) ionic liquids should be of particular interest due to their availability in technical quantities and lower costs compared to their imidazolium-based counterparts. In this article we have shown that ionic liquids can significantly contribute to the chemical industry's initiatives "sustainable development" and "responsible care" when used as performance additives. To the best of our knowledge the use of ionic liquids as secondary dispersant is the first example of an industrial application of ionic liquids as performance additives. *State of the art* universal pigment pastes, which previously could not be used for the tinting of problematic solvent-based coatings and paints, now become applicable to all kinds of coatings and paints by employing ionic liquids. Due to the synergistic effect between ionic liquids and ecofriendly primary dispersants (*e.g.* styrene oxide-based phosphorylated polyethers[20]) the application and utilization of the latter will experience further promotion. Moreover, as in the past problematic solvent-based coatings and paints had to be tinted with solvent-based pigment pastes, the use of ionic liquids in combination with water-based, universal pigment pastes will help to reduce the consumption of VOCs in the future.

## Acknowledgements

The authors would like to thank Kerstin Hell, Angela Rüttgerodt, Andreas Stüttgen and Stefan Silber for their assistance and support.

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‡ Rub-out test: The so-called rub-out test is performed in order to check whether or not a pigment is still well dispersed in the applied coating. For this purpose a portion of the applied coating, which still has to be partly wet, is rubbed with a finger. In the case of a poorly dispersed or even flocculated pigment the mechanical process of rubbing will lead to a homogenous dispersion again. In doing so the desired color strength of the homogeneous mixture is then developed. The color change, respectively the color difference (rub-out value $\Delta E$) between the rubbed and unrubbed part of the coating, is a measure for the performance of the dispersant.

§ Measuring colorimetric values ($L^*$ = brightness): Paper board cards (Lineta® cards) were coated with the tinted (pigmented) paints and coatings. The colors were measured by means of a chromatometer (Type X-Rite, SP 62-162 with a D65/10 illuminant, Company X-Rite) and quantified using CIE (Commisson on Illumination) $L^*a^*b^*$-color system scale ($L^*$ = brightness, $a^*$ denotes the red/green value with a color measurement movement in the +a direction depicting a shift toward red, and $b^*$ denoting the yellow/blue value with a color measurement movement in the +b direction depicting a shift towards yellow). For clarity reasons the $a^*$ and $b^*$ values are omitted in Table 2.

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# Estimation of melting points of pyridinium bromide ionic liquids with decision trees and neural networks†

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*Received 14th June 2004, Accepted 25th October 2004*
*First published as an Advance Article on the web 3rd December 2004*
**DOI: 10.1039/b408967g**

Regression trees were built with an initial pool of 1085 molecular descriptors calculated by DRAGON software for 126 pyridinium bromides, to predict the melting point. A single tree was derived with 9 nodes distributed over 5 levels in less than 2 min showing very good correlation between the estimated and experimental values ($R^2 = 0.933$, RMS = 12.61 °C). A number $n$ of new trees were grown sequentially, without the descriptors selected by previous trees, and combination of predictions from the $n$ trees (ensemble of trees) resulted in higher accuracy. A 3-fold cross-validation with the optimum number of trees ($n = 4$) yielded an $R^2$ value of 0.822. A counterpropagation neural network was trained with the variables selected by the first tree, and reasonable results were achieved ($R^2 = 0.748$). In a test set of 9 new pyridinium bromides, all the low melting point cases were successfully identified.

## Introduction

Ionic liquids (IL) have gained an enormous importance in recent years due to their green and tuneable properties. The negligible vapour pressures allow for their potential use as green substitutes for organic volatile solvents.[1] Judicious choice of anion and cation permits production of IL's with physical and chemical properties fitted to a specific problem.[2] Solubility, polarity, viscosity and melting points are thus of utmost importance, and their estimation from the chemical structure is highly desired to focus synthetic efforts on IL's with the best chances of exhibiting the required characteristics.

Traditionally, chemists have relied on chemical intuition to predict such properties. But in some cases, very subtle features have a tremendous impact on the property. Fig. 1 illustrates such behaviour related to the melting point.

In cases like that, computational tools can analyse experimental data to ferret out hidden relationships between aspects of the chemical structure and the melting point, and propose a predictive model.

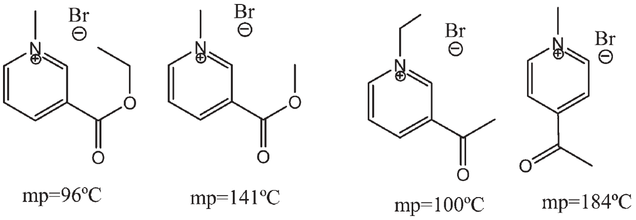

**Fig. 1** Examples of similar chemical structures of pyridinium bromides with highly diverse melting points.

Chemical structures can be numerically encoded by molecular descriptors. Thousands of molecular descriptors have been proposed covering features from constitution to geometry to electronic properties, and they can be easily calculated with available software. Then, relationships between molecular descriptors and the property being predicted can be obtained computationally. Models like neural networks (NN),[3] decision trees,[4] ensembles of trees,[5] partial least squares (PLS)[6] and multiple linear regressions (MLR) are among the most popular. Some linear relationships between molecular descriptors and melting points of ionic liquids were reported in the past.[7,8]

Usually the most important features concerning models obtained from computational tools are the flexibility to model multiple mechanisms of action, the capability to deal with high dimensional data, and the level of predictive accuracy.

Neural networks and decision trees are highly flexible and are able to account for multiple mechanisms of action, while linear methods are more rigid. On the other hand NNs are not so efficient dealing with large sets of variables. Time-consuming genetic algorithms[9,10] are often used to obtain more compact and efficient sets of variables for MLR and neural networks. Decision trees are fast and efficient for high dimensional data, but usually show relatively low prediction accuracy. Accuracy can be significantly improved with ensembles of trees (forests).[11] Classification and regression trees (CART) have recently gained much interest in chemoinformatics, particularly for QSAR studies based on large pools of available molecular descriptors.[5,11–13]

In this paper we report our studies using decision trees and ensembles of decision trees (forests) to model the melting points of a series of 126 pyridinium bromides, as a fast, flexible alternative to linear regressions. Additionally, the potential of the molecular descriptors chosen by the trees to train counterpropagation neural networks (CPG NNs) was investigated.

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† Electronic supplementary information (ESI) available: ensemble of trees grown and list of initial descriptors. See http://www.rsc.org/suppdata/gc/b4/b408967g/

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## Methodology

### Data set

In order to validate the approach, we used the same data set of 126 pyridinium bromides as Katritzky *et al.*[7] with objects organized from the lowest to the highest melting point, comprising a range of melting points between 30–200 °C. The cross-validation was performed according to the Katritzky *et al.*[7] work, with three subsets (set A = 1st, 4th …124th; set B = 2nd, 5th …125th; and set C = 3rd, 6th …126th).

### Molecular descriptors

3D models for the 126 pyridinium cations were obtained using the CORINA 3.0 program,[14–16] and these were submitted to DRAGON 3.0 to calculate the molecular descriptors[17]—1045 molecular descriptors were obtained, after excluding constant or nearly constant descriptors. An additional 40 descriptors were defined to include properties such as Gasteiger charges, and were calculated with PETRA[18] software version 3.1. 3D models generated by CORINA seemed particularly suitable for this study since the software is based on rules derived from a database of crystallographic structures. Descriptors calculated by DRAGON include a) 3D type descriptors, which account for the 3D geometry of the molecule (WHIM,[19] geometrical, RDF,[20] GETAWAY,[21] Randic molecular descriptors, charge indices and aromaticity descriptors); b) 2D type descriptors, related to the connectivity between the atoms of the molecule (including topological descriptors, molecular walk counts, BCUT, Galvez and 2D-autocorrelation descriptors); c) 1D descriptors, which encode structural information like counts of specific functional groups, and atom-centred fragments; and d) 0D descriptors which represent global characteristics of the molecule such as the atomic weight. A list of all descriptors is available in the Supplementary Information.†

### Decision trees

A tree is sequentially constructed, partitioning objects from a parent node into two child nodes. Each node is produced by a logical rule, usually defined for a single variable, where objects below a certain variable's value fall into one of the two child nodes, and objects above fall into the other child node (a graphical representation of a decision tree is presented below in the Results section). The prediction for an object reaching a given terminal node is obtained as the average of the mp of the objects (in the training set) reaching the same terminal node. The entire procedure comprises three main steps. First an entire tree is constructed by data splitting into smaller nodes, each produced split is evaluated by an impurity function[4] which decreases as long as the new split permits the child node's content to be more homogeneous than the parent node. Second, a set of smaller, nested trees is obtained by obliteration (pruning) of certain nodes of the tree obtained in the first step. The selection of the weakest branches is based on a cost-complexity[4] measure that decides which sub-tree, from a set of sub-trees with the same number of terminal nodes, has the lowest (within node) error. Finally, from the set of all nested sub-trees, the tree giving the lowest value of error in cross-validation (where the set of objects used to grow the tree is different from the prediction set) is selected as the optimal tree.

In this study, regression trees were grown with the R program version 1.9.0 using the RPART library with the default parameters.[22] A tree was obtained by submitting the 126 molecules to RPART, each molecule represented by 1085 molecular descriptors. The variables chosen for building the tree (*global tree*) were further evaluated in an additional 3-fold cross-validation procedure. This step employed exactly the same 3 subsets A, B, and C as in the Katritzky *et al.* study.[7] The cross-validation trees were allowed to grow using a) only the variables selected for the global tree, and b) only the objects pertaining to 2 subsets. At the end, predictions were obtained for the third subset (not used for growing the tree).

### Ensemble of trees (forest)

The above described methodology was followed to grow regression trees, but now *n* trees were sequentially grown, instead of only one. The predictions were then obtained by averaging the individual *n* predictions. The *n* trees were grown in the following sequence. The first tree was obtained starting from the entire pool of 1085 descriptors, then the descriptors selected for the first tree were erased from the input file, and this is again submitted to the R program, to construct the second tree. The sequence was repeated until *n* trees were obtained. A 3-fold cross-validation procedure was performed as before, for each of the *n* trees, and the *n* predictions were averaged to obtain cross-validation predictions. Results were obtained for *n* varying between 2 and 10.

### Counterpropagation neural networks

A CPG NN consists of a 2D grid of neurons organized into an input layer and an output layer—Fig. 2 left.[3] Each input neuron has as many elements (*weights*) as there are input parameters, and each output neuron contains as many weights as there are types of outputs. In our case we only have one type of output, the melting point. The network learns by adjusting the weights during a training phase, in which the objects from the training set are repeatedly submitted to the network.

Before the training, the weights are randomly generated. During the training, each object activates the neuron with the most similar input weights to the molecular descriptors of that object—this is the winning neuron. The weights of the winning neuron are adjusted to become even closer to the input vector (molecular descriptors) and the neighbouring neurons are also corrected to approach the input object, with the correction depending on the distance to the winning neuron. The corresponding output weight is also changed to become closer to the experimental value of the property being predicted. The network is trained with all the objects from the training set several times until a predefined number of cycles is reached. Afterward, the network is able to make predictions for new compounds—Fig. 2 right. When a new object (molecule) is submitted, the network activates the winning neuron, and uses the corresponding output weight as the predicted value, in our case the predicted melting point.

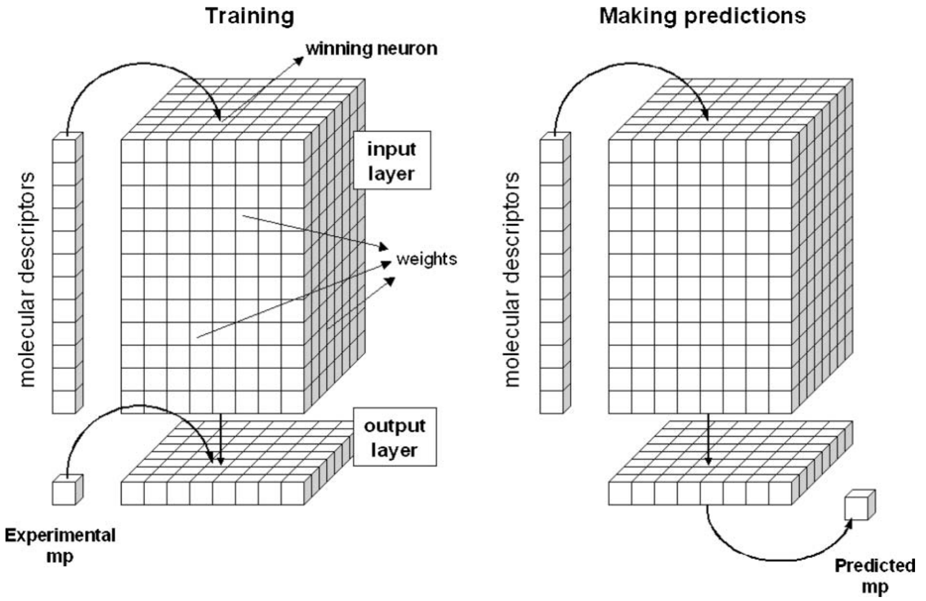

**Fig. 2** Training and prediction procedures in a CPG NN that learns relationships between molecular descriptors and melting points.

In this investigation, CPG NNs were trained using the descriptors selected for the first decision tree. Training and cross-validation were performed with the same subsets as for the decision trees. The molecular descriptors were linearly scaled between 0 and 1. For some experiments (see Results) each descriptor $i$ was multiplied by a factor $L - l_i$, where $L$ is the number of levels in the first tree, and $l_i$ is the distance of the node defined by descriptor $i$ to the root node. CPG NNs were implemented with in-house developed software based on JATOON Java applets.[23,24] The networks (with 12 × 12 neurons for the training set A + B + C and 10 × 10 neurons for the cross-validation experiments) were trained over 100 cycles, using an initial learning span of 5 neurons.

## Results

### Prediction of melting points by a decision tree

From the entire pool of 1085 descriptors for the 126 pyridinium bromides, a regression tree was derived with 9 nodes distributed over 5 levels—Fig. 3 and Table 1. The calculations took less than 2 min using a PC with a Pentium™ IV 2.66 GHz CPU. A good correlation ($R^2$ = 0.933, RMS = 12.61 °C) was obtained between the estimated and experimental values. The results are shown in Fig. 4 and Table 2 and evaluated according to different measures of error. In this application, accurate ranking is probably the most important feature of a predictive model to be used in establishing priorities for laboratory work. The Spearman correlation coefficient was thus included, as it measures the ability to rank objects according to a property.

### Prediction of melting points by ensembles of trees (forests)

Combination of the predictions from an ensemble of regression trees improved the correlation between the predicted and the experimental melting points—Figs. 5 and 6. However, increasing the number of trees ($n$) in the forest further than $n$ = 4 yielded no significant advantage. A 3-fold cross-validation with the ensemble of 4 trees yielded a reasonable match between the predicted and experimental values—$R^2$ = 0.822, Fig. 7. Regression tree models for the 10 grown trees are available in the Supplementary Information.†

### Prediction of melting points by CPG neural networks

The 9 variables selected by the first tree were investigated for their ability to train CPG NNs. We use the decision trees as a tool for a fast detection of relevant variables in order to train CPG NNs. Variables corresponding to nodes near the top of the tree are responsible for large partitions of the data set, while variables far from the root node are responsible for detail partitions. Having this in mind, we performed additional experiments multiplying the descriptors by factors according to the level they occupy in the tree—a factor of 5 for the upper level, 4 for the second level, and so on until the bottom level which gets a factor of 1. The results are shown in Table 3.

### Prediction of melting points for a new set of pyridinium bromides

A new set of 9 objects was obtained from the literature and predictions were made using the previously developed models. The predictions obtained by a single tree and by the ensemble of 4 trees are displayed in Table 4.

Fig. 8 shows the output layer of the CPG NN trained with the weighted descriptors for the 126 objects. The neurons were coloured according to their output values, and the 9 new objects were mapped onto the surface. The activated neurons are identified by the experimental mp of the mapped objects.

## Discussion

The first obtained regression tree is based on 9 molecular descriptors, and exhibits high predictive power. The root node is defined by the G2 descriptor (a gravitational index), which can be related to the size of the molecule—G2 is larger for

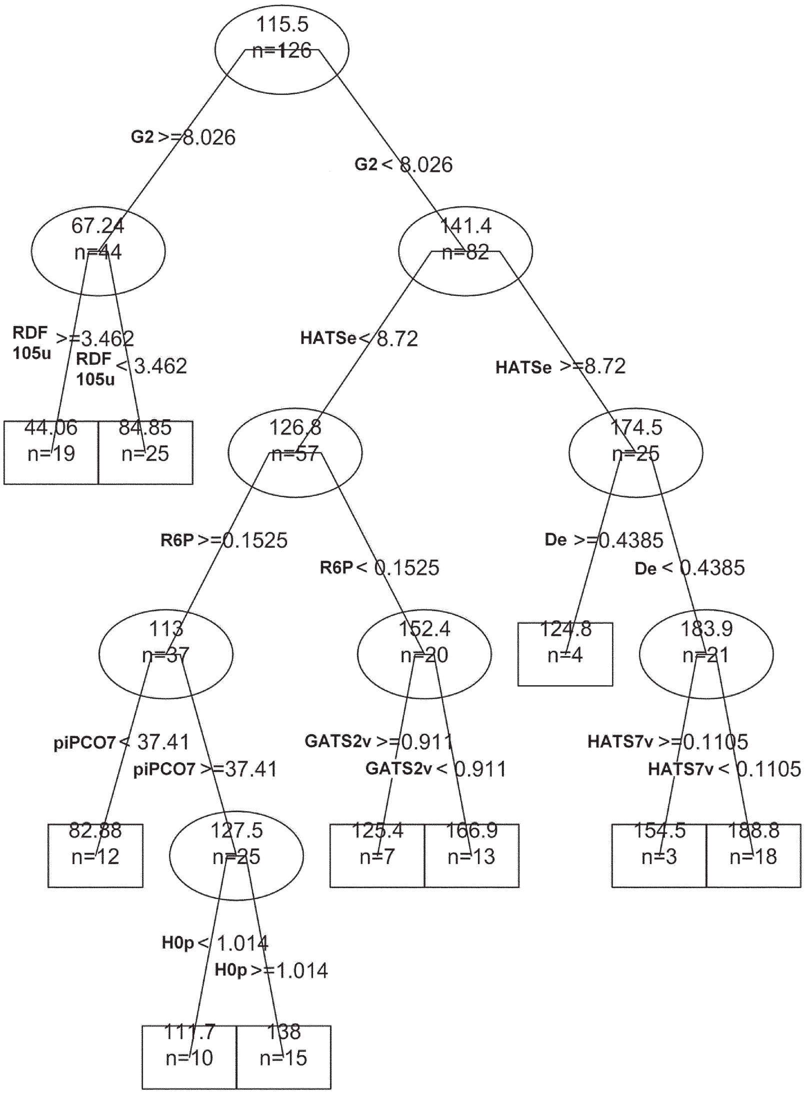

**Fig. 3** Regression tree model obtained for the estimation of melting points. Terminal nodes are represented with rectangles while intermediate nodes are represented with ovals. The number of objects reaching a node, as well as the average of their melting points is displayed inside each node. The rules are displayed near the corresponding nodes using names for the descriptors as defined in Table 1.

**Table 1** Molecular descriptors selected to build a regression tree

| Descriptor | Description |
|---|---|
| G2 | **Geometrical,** G2 is the gravitational index (bond restricted).<br>G2 = $\sum_{ij} \frac{m_i m_j}{r_{ij}^2}$, where the summation goes over all pairs of bonded atoms, $m_i$ is the atomic mass of atom $i$, and $r_{ij}$ is the distance between atoms $i$ and $j$. |
| RDF105u | **RDF,**[20] accounts for the abundance of pairs of atoms at a distance of 10.5 Å. |
| HATSe | **GETAWAY descriptor,**[21] accounts for the influence of individual atoms in the total shape of the molecule combined with electronegativities. HATSe is the leverage-weighted total index weighted by atomic Sanderson electronegativities. |
| R6P | **GETAWAY descriptor,**[21] R6P is the R autocorrelation of lag 6 weighted by atomic polarizabilities. |
| De | **WHIM descriptor,**[19] geometrical descriptor calculated on the projections of the atoms along principal axes. De is total accessibility index weighted by atomic Sanderson electronegativities. |
| piPCO7 | **Topological descriptor,** 2D descriptor, independent of the conformation. piPCO7 is the molecular multiple path count of order 7. |
| GATS2v | **2D Geary autocorrelation,** 2D descriptor, independent of the conformation, obtained by the summation of all products of the terminal atoms of all the paths of path length (lag) 2 weighted by van der Waals volumes. |
| HATS7v | **GETAWAY descriptor,**[21] accounts for the influence of individual atoms in the total shape of the molecule combined with van der Waals volume. HATS7v is the leverage-weighted autocorrelation of lag 7 weighted by atomic van der Waals volume. |
| H0p | **GETAWAY descriptor,**[21] accounts for the influence of individual atoms in the total shape of the molecule combined with atomic polarizabilities. H0p is the H autocorrelation of lag 0 weighted by atomic polarizabilities. |

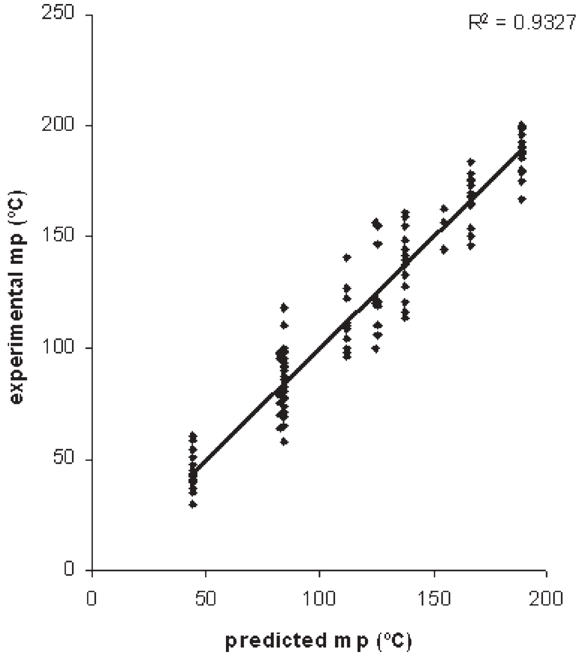

**Fig. 4** Predicted values *vs.* experimental melting points (mp) for the set of 126 pyridinium bromides. Predictions were obtained by a regression tree grown with 126 objects described by 1085 variables.

**Table 2** Predictions[a] obtained by trees, CPG NNs and linear methods for the training set (entire set) and in cross-validation (CV) tests[7]

| | | A + B + C (training set) | A (CV) | B (CV) | C (CV) |
|---|---|---|---|---|---|
| Decision tree | RMS | 12.61 | 22.13 | 28.27 | 26.07 |
| | $R^2$ | 0.933 | 0.794 | 0.662 | 0.711 |
| | $R^{2*}$ | 0.933 | 0.795 | 0.708 | 0.714 |
| | $\bar{e}$ | 10.07 | 15.95 | 21.76 | 18.61 |
| | *SP* | 0.940 | 0.871 | 0.798 | 0.818 |
| CPG NN (trained with weighted descriptors) | RMS | 24.41 | 29.21 | 23.97 | 31.50 |
| | $R^2$ | 0.748 | 0.640 | 0.757 | 0.578 |
| | $R^{2*}$ | 0.762 | 0.661 | 0.783 | 0.592 |
| | $\bar{e}$ | 19.67 | 24.29 | 19.38 | 26.80 |
| | *SP* | 0.871 | 0.789 | 0.901 | 0.754 |
| Ensemble of 3 trees | RMS | 11.41 | 18.79 | 22.06 | 25.42 |
| | $R^2$ | 0.945 | 0.851 | 0.794 | 0.725 |
| | $R^{2*}$ | 0.946 | 0.855 | 0.809 | 0.737 |
| | $\bar{e}$ | 9.420 | 15.33 | 16.82 | 20.06 |
| | *SP* | 0.937 | 0.925 | 0.873 | 0.858 |
| Ensemble of 4 trees | RMS | 10.82 | 17.11 | 20.32 | 23.67 |
| | $R^2$ | 0.950 | 0.877 | 0.825 | 0.772 |
| | $R^{2*}$ | 0.951 | 0.882 | 0.836 | 0.762 |
| | $\bar{e}$ | 8.727 | 13.73 | 15.22 | 18.64 |
| | *SP* | 0.954 | 0.942 | 0.886 | 0.861 |
| Ensemble of 8 trees | RMS | 9.910 | 18.17 | 18.70 | 21.96 |
| | $R^2$ | 0.958 | 0.861 | 0.852 | 0.795 |
| | $R^{2*}$ | 0.960 | 0.870 | 0.880 | 0.812 |
| | $\bar{e}$ | 8.140 | 14.55 | 14.88 | 17.65 |
| | *SP* | 0.962 | 0.934 | 0.913 | 0.910 |
| Multiple linear regression (MLR)[7] | RMS | 23.41 | 27.10 | 25.53 | 24.05 |
| | $R^2$ | 0.788 | 0.769 | 0.779 | 0.757 |
| | $R^{2*}$ | 0.768 | n.a. | n.a. | n.a. |
| | $\bar{e}$ | 18.07 | n.a. | n.a. | n.a |
| | *SP* | 0.871 | n.a. | n.a. | n.a. |

[a] RMS is the root mean square of errors; $R^2$ is the goodness of fit correlation coefficient; $R^{2*}$ is the square of the Pearson correlation coefficient; $\bar{e}$ is the mean error, and *SP* is the Spearman correlation coefficient.

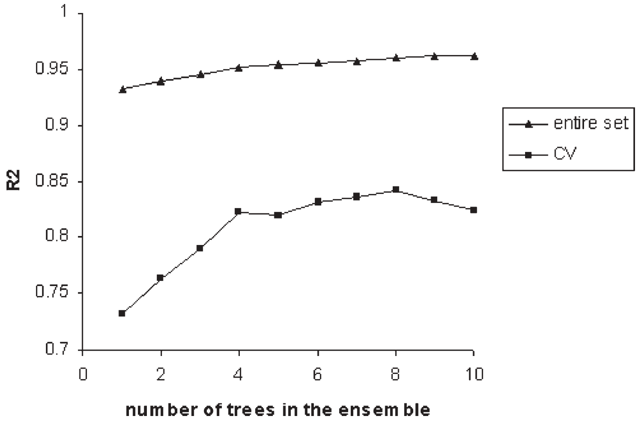

**Fig. 5** Influence of the size of the forest on the quality of mp predictions, growing the trees with the whole data set, or in a 3-fold cross-validation procedure.

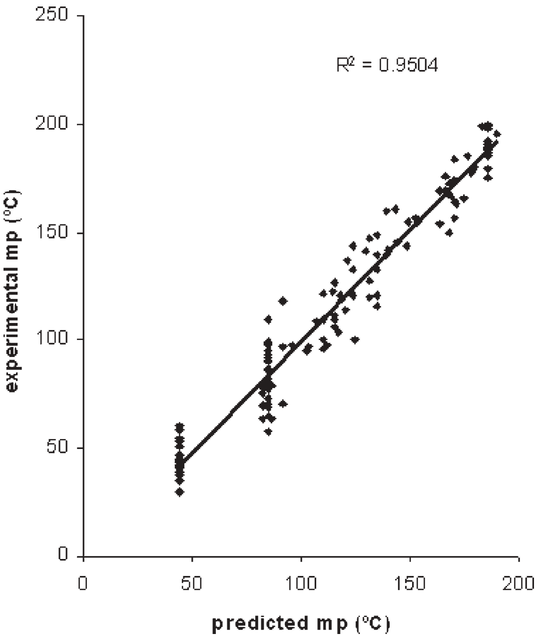

**Fig. 6** Predicted *vs.* experimental melting points (mp) for the set of 126 pyridinium bromides. Predictions were obtained by averaging predictions from 4 regression trees grown using the 126 objects.

large molecules. The first node assigns low melting points to compounds with high G2 index. This descriptor was not selected by Katritzky *et al.*'s approach[7] although it was certainly available in the initial pool of descriptors—the lack of a linear relationship between the gravitational index and the mp probably prevents a linear approach to using it. Interestingly, the G2 descriptor was found to be highly correlated with boiling points in a set of 298 organic compounds, although in the opposite direction.[25] Further partition of the left node (low melting points) is based on the RDF descriptor at 10.5 Å, which is clearly related to long chains—detection of pairs of atoms with an interatomic distance of 10.5 Å.[20] In this data set, the presence of alkyl chains longer than C8 are indeed associated with melting points at the lower end of the range (<60 °C).[26]

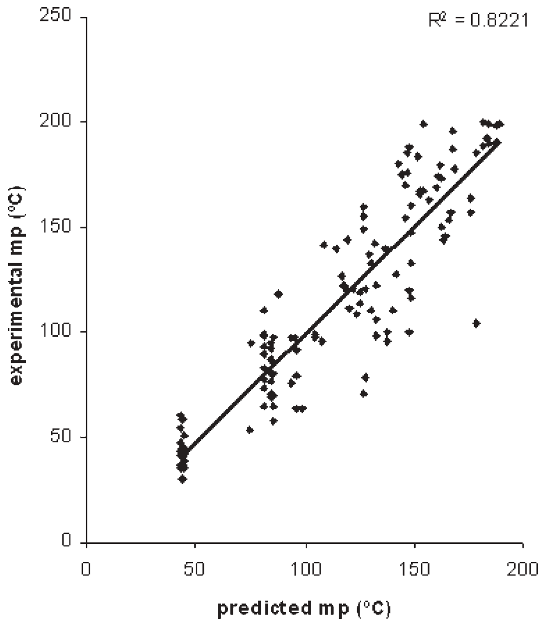

**Fig. 7** Predicted *vs.* experimental melting points (mp) for the set of 126 pyridinium bromides with a 3-fold cross-validation procedure on an ensemble of 4 regression trees.

**Table 3** Prediction of melting points by CPG NNs trained with unweighted and weighted descriptors selected by the trees

| | Tree descriptors $R^2$ | Tree descriptors (weighted) $R^2$ |
|---|---|---|
| Prediction for the training set (A + B + C) | 0.653 | 0.748 |
| CV—prediction for test set A | 0.475 | 0.640 |
| CV—prediction for test set B | 0.627 | 0.757 |
| CV—prediction for test set C | 0.406 | 0.578 |

The descriptors involved in the right main branch of the tree are more difficult to interpret. Most of the selected descriptors are 3D descriptors, particularly GETAWAY descriptors, which are calculated from a single molecular conformation. This reinforces our initial proposal that 3D structures generated by CORINA are useful, and that working with a single conformation is realistic since the melting point can be viewed as a property of a solid. GETAWAY descriptors account for the influence of individual atoms on the shape of the molecule, and are often combined with atomic properties such as electronegativities, polarizabilities or van der Waals volumes.[21] GETAWAY descriptors have been successful for the prediction of melting points of polycyclic aromatic hydrocarbons and polychlorinated biphenyls.[27] The other 3D descriptor is a WHIM descriptor, namely the total accessibility index weighted by atomic Sanderson electronegativities. WHIM descriptors were designed to capture 3D information regarding molecular size, shape, and symmetry and atom distribution with respect to the molecule as a whole.[19] The De descriptor is a compactness descriptor, which encodes information about the distribution of electronegativities along the three axes of the molecule. Another size directional WHIM index was selected in a QSPR model to predict melting points of polychlorinated biphenyls.[28]

The piPCO7 descriptor isolates a group of 12 compounds with relatively low melting point (average = 83 °C). This descriptor counts paths of order 7 and at the same time is influenced by multiple bonds. In fact, most of the isolated 12 compounds have no multiple bonds outside the pyridinium ring, and most of the 25 compounds in the right child node have a functional group with a multiple bond.

The accuracy of the predictions was significantly improved by combining several trees in an ensemble—Fig. 5 and Table 2. We chose the ensemble with 4 trees as the optimum, since after that point no significant improvement in predictive ability can be observed. This forest model accurately fits the experimental data ($R^2$ = 0.950, RMS = 10.82 °C), and performs well in cross-validation tests ($R^2$ = 0.877, 0.825, 0.772, respectively for sets A, B, and C). Interpretation of these results should take into account the difficulty of modelling melting points of organic salts, and the fuzziness associated with such data—differences of 10–15 °C in the reported mp for the same compound from different authors are not uncommon in the literature. An $R^2$ value of 0.950 compares to the value of 0.788 obtained by Katritzky *et al.*[7] and the value of 0.790 obtained by Eike *et al.*[8] This better fitting of the entire set (after the entire set was used to develop the model) may be due to the higher flexibility of the decision trees and the larger number of descriptors employed. A more significant comparison can be obtained with cross-validation tests using the same subsets as Katritzky *et al.* (Table 2)—the ensembles of trees yielded slightly better correlations than the linear methods. However, it must be emphasized that it is not possible to rigorously compare the two methods without an external set, even if the procedures here described for variable selection and cross-validation were designed to follow as much as possible those described in the previous studies. Essentially the quality of predictions by trees and MLR are not very different.

**Table 4** Predictions for the new set of objects using a single tree and the ensemble of 4 trees

| Pyridinium bromide | Experimental mp/°C | Decision tree | Ensemble of 4 trees |
|---|---|---|---|
| 1-(2-Oxo-butyl)-pyridinium | 180 ref. 29 | 138 | 122 |
| 1-(3-Methyl-2-oxo-butyl)-pyridinium | 149 ref. 29 | 138 | 139 |
| 1-Isobutoxycarbonylmethyl-pyridinium | 87 ref. 29 | 85 | 84 |
| 1-(2-Dodecanoyloxy-ethyl)-pyridinium | 80.5 ref. 30 | 44 | 44 |
| 1-(2-Hexadecanoyloxy-ethyl)-pyridinium | 80 ref. 30 | 44 | 44 |
| 1-(2-Icosanoyloxy-ethyl)-pyridinium | 81 ref. 30 | 44 | 44 |
| 3,4-Dihydroxy-2-(1-hydroxy-ethyl)-1-methyl-pyridinium | 142 ref. 31 | 125 | 108 |
| 1-Benzyl-3-(2-oxo-oxazolidine-3-carbonyl)-pyridinium | 109 ref. 32 | 85 | 84 |
| 1-Benzyl-3-dimethylcarbamoyl-pyridinium | 158.5 ref. 32 | 85 | 84 |

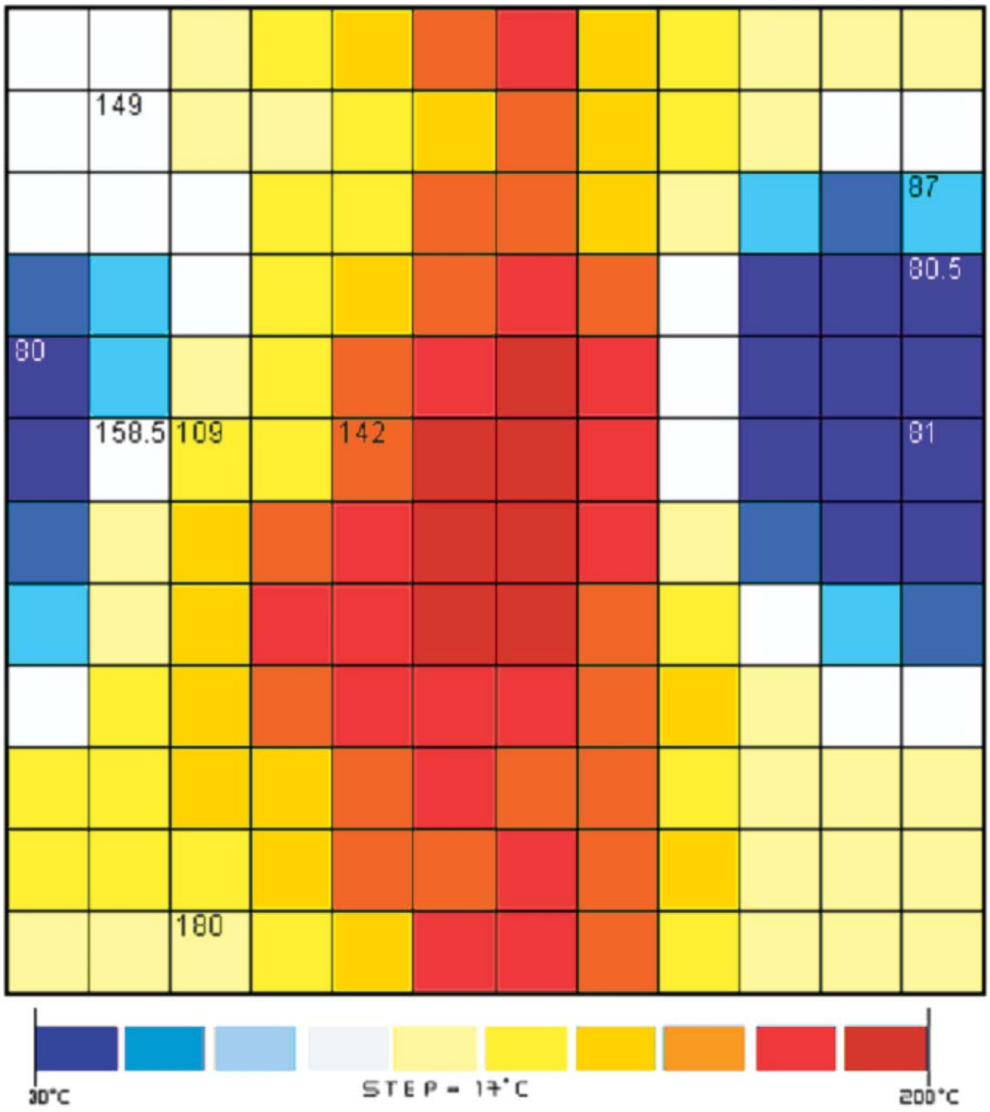

**Fig. 8** Mapping of the 9 new objects onto the output layer of a CPG NN (see text). The labels shown in the map correspond to experimental mp values of the nine objects. Low mp objects were correctly identified by exciting neurons in the blue region.

Although the ensemble of 4 trees employs 35 descriptors (9 descriptors in the first tree, 9 in the second tree, 8 in the third tree, and 9 in the fourth tree), this number overstates the real amount of information encoded by the set of descriptors. In fact, the architectures of the 4 trees overlap to a large extent, and the 4 trees use descriptors which are in most cases highly correlated, *i.e.* the descriptors do not change much from tree to tree, even if they are not exactly the same. The left main branch of the trees (leading to low mp predictions) is particularly similar in all the 4 trees, with almost the same content in the terminal nodes (it is constructed by descriptors related to molecular size). This explains why the ensemble predicts the same value for all the low melting point compounds—all of them get the same prediction in all trees.

Interestingly, the second tree exhibits two nodes under the right main branch defined by information content of order 1 descriptors ($^1$CIC and $^1$IC). These two descriptors describe the connectivity of one molecule in terms of symmetry. Information content descriptors were selected both in the Katritzky *et al.* and Eike *et al.* works, and an inverse relationship between the melting points and the information content descriptors was also observed. This fact can be interpreted as low-symmetry molecules, which have low coordination ability, having low melting points.[7]

An additional experiment has shown that exclusion of highly intercorrelated descriptors from the initial pool (with Pearson correlation coefficient above 0.8) does not lead to improved predictions.

Tree construction can also be seen as a very fast method for selecting relevant variables. However, descriptors that are successfully employed by trees are not necessarily successful for CPG NNs, because the two methods use the descriptors in radically different ways. In trees, descriptors are used sequentially, some to make decisions involving all the objects, others only in small branches for a few objects. In opposition, CPG NNs always use all the descriptors simultaneously for all the objects.

CPG NNs were trained with the 9 descriptors selected by the first tree, and reasonable results could be achieved, particularly if the descriptors were weighted according to the level where they are used in the tree. The predictions were not as accurate as with the trees, but comparable to the MLR models in terms of some criteria.

Beyond predictive accuracy, CPG NNs are interesting because they provide information regarding the topology of the data. Mapping an object into a CPG NN also allows for retrieval of other objects that were mapped onto the same region, and that can to some extent explain and support the prediction. Visualisation of the output weights (Fig. 8) reveals several regions on the surface corresponding to different ranges of melting points. It is a representation of the combined relationship between the selected descriptors and the melting point of pyridinium bromides. When applied to the test set of 9 new compounds, the network mapped those with lower melting points onto dark blue neurons, and one salt with low melting point (87 °C) onto a light blue neuron. This means the network would correctly identify the salts with highest potential as ionic liquids.

The decision tree and the ensemble also recognized the low melting point objects in the test set (Table 4). The accuracy of other predictions varied. The wrong assignment of a low melting point (80–85 °C) to a salt with mp = 158 °C is the worst prediction in the set. However, for this application, a false positive (false prediction of an ionic liquid) is certainly preferable to a false negative (missing a compound with ionic liquid properties).

## Conclusion

Regression trees were able to build good predictive models for the melting points of pyridinium bromides from the molecular structure. The quality of the predictions could be improved by using an ensemble of trees (forest) instead of a single tree, and the results compared well to linear regressions previously reported in the literature for the same data set. Regression trees are alternative methods, which are flexible, extremely fast to develop, and can easily screen large numbers of descriptors. Trees also showed some success as a fast method for selection of variables for neural networks. Reasonable qualitative results were obtained for a new 9 compound set, with all the low melting point objects being recognized by the decision tree, the ensemble of trees and the CPG neural networks. The described methods make use of widely available software tools and are of general applicability.

## Acknowledgements

The authors thank Fundação para a Ciência e Tecnologia (Lisbon, Portugal) and FEDER fund for financial support.

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# Oxidation of 2,4,6-trichlorophenol by hydrogen peroxide. Comparison of different iron-based catalysts†

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*Received 23rd July 2004, Accepted 19th October 2004*
*First published as an Advance Article on the web 25th November 2004*
**DOI: 10.1039/b411269e**

A systematic study of the stoichiometric and kinetic efficiencies of catalysts in the oxidation of 2,4,6-trichlorophenol by hydrogen peroxide was carried out. Six different iron-based activators were used: $Fe^{3+}$(aq), $Fe(TPPS)^+$, *cis*-$[(cyclam)Fe]^{3+}$, *trans*-$[(cyclam)Fe]^{3+}$, $[Fe(TPA)]^{2+}$, and $[Fe(6\text{-}Me_2\text{-}TPA)]^{2+}$ (ligand abbreviations: TPPS = *meso*-tetra(4-sulfonatophenyl) porphine, cyclam = 1,4,8,11-tetraazacyclotetradecane, TPA = tris(2-pyridylmethyl)amine, 6-$Me_2$-TPA = bis[(6-methyl-2-pyridyl)methyl](2-pyridylmethyl)amine). The stoichiometric efficiencies of the catalyst were characterized by comparing the total organic carbon content, chloride ion concentration, and remaining oxidant concentration to the ideal stoichiometry where carbon dioxide, water and inorganic chloride are the only products. The kinetic efficiencies of the catalysts were compared using the rate of chloride ion formation and $H_2O_2$ consumption. It was shown that $Fe(TPPS)^+$ is the best catalyst. Illumination by visible light significantly enhances the rate of oxidation.

## Introduction

Polychlorinated phenols are used as wood preservatives, pesticides, fungicides, herbicides, insecticides or disinfectants, and they are also present in the waste of paper mills. These compounds are highly toxic, persistent, and regarded as priority pollutants for which efficient chemical treatment processes are needed.[1–4] Oxidative degradation is probably the most advantageous reaction type for this purpose and several different methods have been reported including $H_2O_2$-dependent homogeneous catalysis,[1–12] $TiO_2$-based systems for photodegradation,[13–16] ozonization,[17] and bacterial methods.[18–20]

2,4,6-Trichlorophenol (TCP) is one of the most significant pollutants among chlorinated phenols and is often used to test the efficiency of oxidation methods.[1,3] These methods usually use $H_2O_2$ or $KHSO_5$ as a stoichiometric oxidant. Aqueous $H_2O_2$ is generally regarded as an environmentally friendly, "green" reagent[21–27] partly because it gives water as the sole by-product of oxidation. However, $H_2O_2$ does not oxidize TCP or other chlorinated phenols in the absence of catalysts.[28] The activators are usually transition metal complexes, most often iron(II) or iron(III) complexes involving N-donor ligands.[1–12]

Collins and co-workers recently reported the use of an oxidatively robust iron(III) complex of a TAML (*t*etra *a*mido *m*acrocyclic *l*igand) for the oxidation of TCP.[3] Meunier and co-workers used iron tetrasulfophthalocyanine[1] and iron(III) porphine derivatives.[5,6] These complexes have a common feature: all of them have 4 N donor atoms in a planar arrangement surrounding the iron center. Iron-based non-heme activators for $H_2O_2$ are also being developed and studied for the epoxidation of olefins.[29–33] We postulated that these might also be successful in the oxidation of TCP. Que and co-workers used iron complexes of tripodal polypyridyl ligands and they found characteristic differences between the catalytic activity of high-spin and low-spin iron(II) complexes which otherwise were very similar.[30–32] Iron(III) cyclam complexes have also been successfully used to activate $H_2O_2$ toward epoxidation of olefins.[29] Two separable isomers of the iron(III) cyclam complex are known: the *cis* complex is high-spin, the *trans* complex is low-spin.[34]

In this work, we present a systematic study of the efficiencies of iron catalysts in the aqueous oxidation of TCP by $H_2O_2$. Six different complexes were used (HS: high-spin, LS: low-spin): $Fe(TPPS)^+$ (LS), *cis*-$[(cyclam)Fe]^{3+}$ (HS), *trans*-$[(cyclam)Fe]^{3+}$ (LS), $[Fe(TPA)]^{2+}$ (LS), $[Fe(6\text{-}Me_2\text{-}TPA)]^{2+}$ (HS), and $Fe(H_2O)_6{}^{3+}$ (HS) for comparison. The structural formulas of the ligands are shown in Chart 1. We report the development

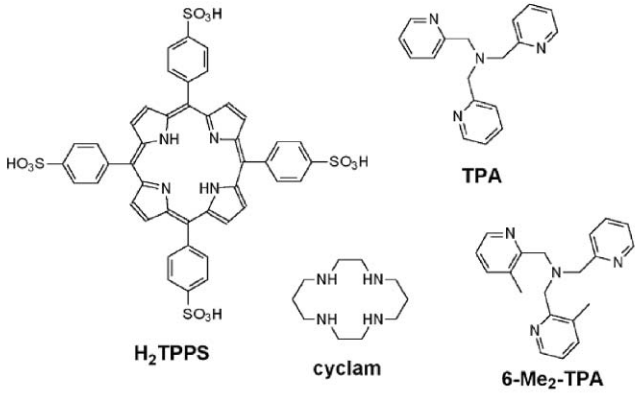

**Chart 1** Ligands used in this study.

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† Electronic supplementary information (ESI) available: additional experimental observations. See http://www.rsc.org/suppdata/gc/b4/b411269e/

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of several methods to characterize and compare the stoichiometric and kinetic efficiencies of the different catalysts.

## Results and discussion

### General considerations

In an ideal case, the total oxidation of TCP by $H_2O_2$ should produce only water, carbon dioxide, and inorganic chloride:

$$C_6H_3Cl_3O + 11H_2O_2 \rightarrow 6CO_2 + 11H_2O + 3H^+ + 3Cl^- \quad (1)$$

However, the known methods do not oxidize TCP totally. Organic compounds, most often dicarboxylic acids such as oxalic acid, malonic acid, chloromalonic acid, maleic acid, and chloromaleic acid, are usually detected as the final products.[1,3] The efficiency of an oxidation method can be characterized by comparing its actual stoichiometry with the ideal case indicated in eqn. 1.

One method often used to characterize the final organic product distribution is GC-MS.[3] This method usually requires considerable sample treatment, which, together with possible secondary reactions on the GC column, can potentially introduce considerable error.[35] In addition, reliable quantification of GC-MS data requires time consuming calibration for each organic component measured. Used with caution, GC-MS can still be a highly valuable source of information on the organic products. Our GC-MS experiments did not prove any formation of highly toxic dioxins at any time, which is of particular concern in chlorophenol oxidations in general.[3] This is probably the only really important piece of information from GC-MS studies for the purposes of this work, as the overall stoichiometric efficiency involves mostly inorganic substances (see eqn 1), which cannot be analyzed by this method. After describing our observations on the choice of oxidant and the possible use of buffers, this paper will summarize our efforts to develop methods to characterize the stoichiometric and kinetic efficiency of catalytic TCP oxidation with special emphasis on the environmentally relevant aspects of the process.

### Choice of oxidant

The stoichiometric oxidant of a green oxidation process should be readily available and give minimal amounts of by-products. $H_2O_2$ is ideal in this respect because its reduced form is water. One possible problem with the use of $H_2O_2$ is that under certain conditions it decomposes and iron complexes, which are used as activators, often catalyze this decomposition.[36,37] This may lead to disadvantageous consumption of additional peroxide reagent during the oxidation process.

We also tested $KHSO_5$ as an oxidizing agent for TCP in a few experiments. $KHSO_5$ can often be used as an inexpensive alternative to $H_2O_2$ in organic transformations, and its use was preferred even in TCP oxidation in a few earlier studies.[5] Although reactions with $KHSO_5$ were usually faster than those with $H_2O_2$ and the same catalyst, a major problem was revealed by monitoring the concentration of $Cl^-$ formed in the reaction. After its initial formation, a decrease was detected in $Cl^-$ concentration during the oxidation process. To identify the reaction responsible for the decrease, experiments were carried out using $Cl^-$, $KHSO_5$ and $Fe(TPPS)^+$ as a catalyst (without the addition of TCP). A substantial decrease was detected in $Cl^-$ concentration (see Electronic Supplementary Information†), and the formation of chlorine was confirmed. Thus, $KHSO_5$ oxidizes the $Cl^-$ formed in the primary reaction to $Cl_2$ under catalytic conditions. This procedure is disadvantageous because it consumes additional oxidizing agent and produces a toxic gas. The use of $KHSO_5$ also has the inherent disadvantage of forming considerable amounts of $K_2SO_4$ as a by-product. It is concluded that $H_2O_2$ is a more environmental friendly oxidizing agent for the oxidation of chlorinated phenols.

### Possible use of buffers

Buffers are often used in laboratory studies on the oxidation of chlorophenols.[1,2,5–7] However, the use of buffers in real waste treatment methods would be rather disadvantageous. It is thus arguable that the laboratory studies should be done without additives such as buffers. In fact, the use of buffers in laboratory studies is a potential source of misleading conclusions for two common, but often overlooked reasons: possible oxidation of the buffer and complexation of the catalyst by the buffer. Because the buffer is typically present at a concentration at least an order of magnitude higher than any substrate, these processes can be very significant even if they are relatively slow or the interactions are not very strong. Indeed, the non-innocent role of phosphate buffers during TCP oxidation has been reported earlier.[7]

In our experiments, we have shown that the presence of citric acid, a common buffer compound,[5,6] inhibits the $Fe(TPPS)^+$-catalyzed oxidation of TCP (see ESI†). In agreement with the considerations presented at the beginning of this section, we did not use buffers in this study. In a few examples, the acidity of the solutions was monitored with a pH electrode. These measurements showed that the original pH of the TCP solutions (about 5.5) decreased during the oxidation to 3.2–2.8 depending on the exact initial concentrations. This showed that acid is produced in the reaction as shown in eqn. 1. However, this pH change did not cause any dramatic change in the activity of the catalysts used in this study.

### $^2$H NMR experiments

One possibility to characterize the stoichiometric efficiency of TCP oxidation is to monitor the hydrogens of the original TCP throughout the process. $^1$H NMR is generally not suitable for this purpose because the catalysts are usually paramagnetic, and $H_2O_2$ is not readily available in a deuterated form. However, the use of isotopically-labelled TCP-$d_2$ and $^2$H NMR offers clear advantages.[38,39] Note that $^2$H is a quadrupolar nucleus and $^2$H NMR spectra are thus not sensitive to the presence of paramagnetic catalysts at the concentration levels used in this study.

$^2$H NMR experiments were carried out using a saturated aqueous solution of TCP-$d_2$ ($\sim$2.2 mM), in which the only detectable signals were those of TCP-$d_2$ and HDO, the latter from the natural isotope distribution of hydrogen in solvent water. After the addition of $H_2O_2$ and the catalyst, the intensity of the signal of TCP-$d_2$ decreased, the intensity of the HDO signal increased gradually. Only the HDO signal was detectable after *ca.* 12 h. This shows that all the hydrogens present in the initial TCP were oxidized to water or became exchangeable (OH or $CO_2H$) protons. No separate signal corresponding to a $^2H$-containing intermediate was detected in these experiments.

A few $^2H$ NMR experiments were carried out with the standard $CD_3CN$ added directly to the solution rather than used as an external standard. In these experiments, clear evidence was found for the oxidation of $CD_3CN$ as well: the intensity of its signal decreased whereas the intensity of the HDO signal increased. This observation further emphasizes that oxidation of added organic substances including buffers or standards may be a serious concern during TCP oxidation.

### Comparison of the efficiencies of different catalyst

The overall stoichiometric and kinetic efficiency of the six different catalysts mentioned in the introduction were compared in systematic studies. It is known that the oxidation of TCP and other chlorophenols is influenced by light, including the room lights of a laboratory.[28] Most of the experiments were carried out in the dark to avoid the interference of light. However, some measurements were also carried out under deliberate illumination to study the effect of light on the stoichiometric and kinetic efficiencies.

### Stoichiometric efficiencies

A series of experiments under standardized conditions (1.63 mM TCP, 136 mM $H_2O_2$, and 30 mg $L^{-1}$ of catalyst) was carried out to compare the stoichiometric efficiencies of the catalyst studied in this work. The mass concentration of the different catalysts was kept constant in these measurements because this is more likely to be important for possible applications than the molar concentration. These conditions were chosen primarily because of solubility issues, the most serious limitation being the solubility of TCP (around 2 mM).

Before performing the test runs, separate experiments, in which the concentration of a TCP stock solution was followed spectrophotometrically, were carried out to exclude any possible aqueous self- or light-induced decomposition of TCP. In these experiments, there was no measurable decrease in the TCP concentration over 2–3 months.

Samples were prepared by adding a solution of $H_2O_2$ to a solution of TCP, and the reaction was initiated by adding the catalyst. To make sure that all processes go to completion, the samples were stored at room temperature in the dark for 10 days before analysis in a sealed glass container that was opened three times during this period to allow gases to escape. After this time, the samples were analyzed for total organic carbon (TOC) content, $Cl^-$ concentration and $H_2O_2$ concentration. The catalyst $Fe(TPPS)^+$ was used in two batches of experiments. In the first, the samples were stored in the dark similarly to other samples. In the second, the samples were illuminated with a 500 W halogen lamp for the first day and then stored in room light.

The TOC of the oxidized sample was considerably lower than that of the original sample in each case. This clearly indicates that carbon dioxide (or less likely carbon monoxide) was formed during the process. Results for the different catalysts are shown in Fig. 1, where the decrease of TOC is shown relative to the initial TCP sample. The higher the decrease, the more carbon dioxide is formed and the more efficient the oxidation is. The best catalyst is $Fe(H_2O)_6^{3+}$, with a TOC decrease of 58%; the others gave slightly lower decreases, 35–45%. The TOC decrease values given in Fig. 1 were calculated assuming that the TOC reduction occurs only because of TCP decomposition, and not because of the oxidation of the organic ligand present in the catalyst (which accounted for only a small fraction, less than 10% of the TOC of the original solution). The observational basis of this assumption was that we did not see significant loss of TOC in experiments where no TCP was used, *i.e.* the organic-containing iron-catalyst was reacted with hydrogen peroxide.

The chloride yield, defined as the amount of chloride ion in the final solution relative to the original total organic chlorine content, was also used to characterize the stoichiometric efficiencies. Fig. 2 shows that chloride yields are generally better than 90% and in two cases are quantitative (*i.e.*, 100%) within experimental error. This shows that chlorine is removed from the organic compounds quite efficiently and little chlorinated organics or chlorinated aromatics remain in the solution after the oxidation. The only exception is

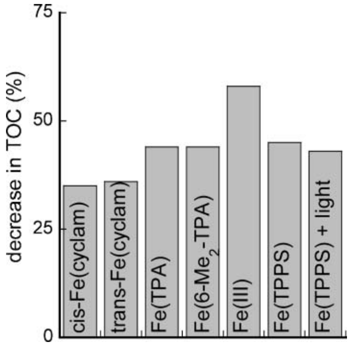

**Fig. 1** Decrease in total organic carbon content during the oxidation of 2,4,6-trichlorophenol with $H_2O_2$ using different catalysts. Initial concentrations: [TCP] = 1.63 mM, $[H_2O_2]$ = 136 mM, [catalyst] = 30 mg $L^{-1}$; reaction time: 10 days; room temperature.

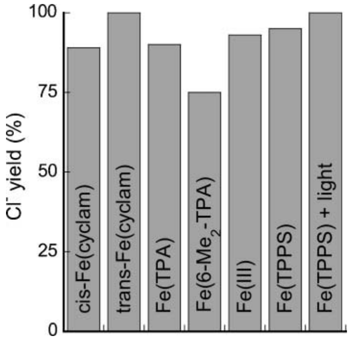

**Fig. 2** Chloride ion yield during the oxidation of 2,4,6-trichlorophenol with $H_2O_2$ using different catalysts. Initial concentrations: [TCP] = 1.63 mM, $[H_2O_2]$ = 136 mM, [catalyst] = 30 mg $L^{-1}$; reaction time: 10 days; room temperature.

$Fe(6\text{-}Me_2TPA)^{2+}$, where the chloride yield is only 75%. This value is significantly different from that determined for $Fe(TPA)^{2+}$ (90%). The difference is not unexpected as these catalysts are known to have different reactivity patterns in epoxidation studies.[31]

The concentration of $H_2O_2$ remaining in the samples was also determined by iodometric titration.[40] Fig. 3 shows the amount of $H_2O_2$ consumed relative to the amount originally added. Under the standardized initial concentrations, the quantitative $H_2O_2$ consumption according to eqn. 1 is 13% and the determined values are usually close to or somewhat lower than this limit. The oxidant consumption was much higher in two cases: 25% for $Fe^{3+}$(aq) and 64% for $Fe(TPA)^{2+}$. Extra consumption of $H_2O_2$ is possible through its decomposition to water and dioxygen. It is concluded that a considerable amount of $H_2O_2$ is lost to catalytic decomposition when $Fe^{3+}$(aq) or $Fe(TPA)^{2+}$ is used as a catalyst. In the case of $Fe(TPPS)^+$ and the two cyclam complexes, data for TOC, chloride ion, and oxidant consumption show that catalytic decomposition cannot be a major source of $H_2O_2$ loss.

In summary, the $H_2O_2$ consumption is the only really significant difference between the catalysts in terms of overall stoichiometric efficiency. The catalyst systems based on tripodal polypyridyl ligands—$Fe(TPA)^{2+}$ and $Fe(6\text{-}Me_2TPA)^{2+}$—are probably less efficient than the others because $Fe(TPA)^{2+}$ consumes a significant quantity of $H_2O_2$ in reactions not involved in the catalytic oxidation, whereas $Fe(6\text{-}Me_2TPA)^{2+}$ leaves considerable chlorinated organics in the system. It should also be noted that the stoichiometric efficiency of $Fe^{3+}$(aq) is comparable to other catalysts. Light does not have significant effects on the stoichiometric efficiency.

## Kinetic efficiencies

The kinetics of the oxidation process could be followed by two independent methods: measurement of the rates of $Cl^-$ formation and $H_2O_2$ consumption. All catalysts were studied in experiments using the same standardized conditions, but the initial concentrations were somewhat different from those used in the stoichiometric efficiency studies. The mass concentration of the different catalysts was kept constant.

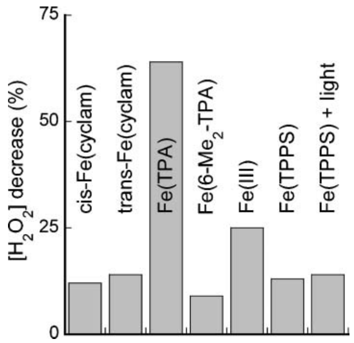

**Fig. 3** Hydrogen peroxide consumpsion during the oxidation of 2,4,6-trichlorophenol with $H_2O_2$ using different catalysts. Initial concentrations: [TCP] = 1.63 mM, $[H_2O_2]$ = 136 mM, [catalyst] = 30 mg $L^{-1}$; reaction time: 10 days; room temperature.

The rate of chloride ion formation was characterized in terms of the half-times ($t_{1/2}$) necessary to reach a chloride ion concentration corresponding to half the total organic chlorine content of the original solution. It should be noted that this quantity is not completely analogous to half lives because the chloride ion formation did not follow an exponential (first-order) curve. Still, $t_{1/2}$ values are suitable for the semi-quantitative comparison of different catalysts, as shown in Fig. 4. Three of the catalysts are similar, with $t_{1/2}$ *ca.* 16–18 h. $Fe(6\text{-}Me_2\text{-}TPA)^{2+}$ is slower than other systems, $t_{1/2}$ *ca.* 24 h, whereas $Fe(H_2O)_6^{3+}$ is somewhat faster, $t_{1/2}$ = 12.6 h. Without doubt $Fe(TPPS)^+$ is the fastest ($t_{1/2}$ = 4.5 h), and illumination with visible light further lowers $t_{1/2}$ to <1 h. These experiments were done using the different catalysts with the same mass concentrations. If molar concentrations are considered, the advantage of $Fe(TPPS)^+$ is even larger because it has the highest molecular weight. It is also seen that light considerably enhances the rate of chloride ion formation and most likely the rate of overall oxidation.

It was also possible to follow the time course of $H_2O_2$ concentration by taking samples from a reaction mixture and determining the concentration of $H_2O_2$. The results from an experiment series with $Fe^{3+}$(aq) as a catalyst are shown in Fig. 5. Experiment *a* was carried out under usual TCP

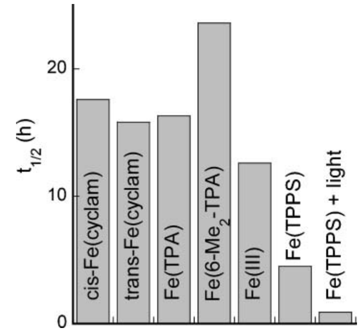

**Fig. 4** The time ($t_{1/2}$) needed to reach 50% $Cl^-$ yield during the oxidation of 2,4,6-trichlorophenol with $H_2O_2$ using different catalysts. [TCP] = 1.61 mM; $[H_2O_2]$ = 95 mM; [catalyst] = 50 mg $L^{-1}$; $\mu$ = 0.1 M ($NaNO_3$); $T$ = 25.0 °C.

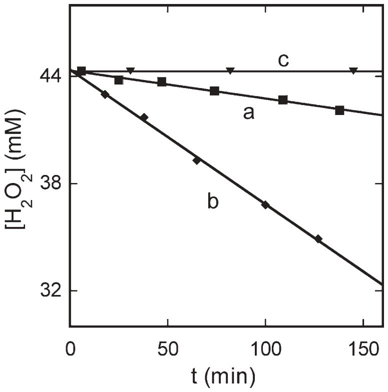

**Fig. 5** Concentration of $H_2O_2$ as a function of time during the oxidation of 2,4,6-trichlorophenol with $H_2O_2$ catalyzed by $Fe^{3+}$(aq). [TCP] = 1.01 mM (a, c), 0 (b); $[Fe^{3+}(aq)]$ = 160 μM (a, b), 0 (c); $T$ = 25.0 °C.

oxidation conditions. In experiment *b*, no TCP was added, and the rate of $H_2O_2$ consumption was clearly faster, an interesting fact that will be interpreted later. Experiment *c* was carried out without the addition of the catalyst. No $H_2O_2$ consumption was detected in this experiment showing once again that TCP is not oxidized by $H_2O_2$ without catalysts.

This series of experiments was repeated with every catalyst. The ratios of the initial rates measured in the presence ($v_{TCP}$) and absence ($v_{blank}$) of TCP were used as a semi-quantitative indicator. Fig. 6 shows these ratios for every catalyst. Ratios span a large range from 54 for $Fe(TPPS)^+$, through 5–10 for the cyclam complexes, to 0.16–0.21 for $Fe^{3+}(aq)$, $Fe(TPA)^{2+}$ and $Fe(6\text{-}Me_2\text{-}TPA)^{2+}$. The last three catalysts had the same value within experimental error.

$Fe(TPA)^{2+}$ induced a sudden burst of $H_2O_2$ decomposition with intense formation of bubbles. This initial burst was over in a few minutes and then a relatively slow decrease in $H_2O_2$ concentration was detected (see ESI†). No similar results were obtained with $Fe(6\text{-}Me_2\text{-}TPA)^{2+}$, which again shows that these two catalysts are dissimilar. The slowly decreasing region was used for evaluation with $Fe(TPA)^{2+}$, because chloride ion kinetic measurements show without doubt that oxidation of the substrate occurs in this stage. The initial burst of $H_2O_2$ decomposition can likely be attributed to the catalyst in its original form accelerating the decomposition of $H_2O_2$ efficiently, but then being transformed to another form during the first few minutes.

It is well known that the decomposition of hydrogen peroxide is sensitive to experimental conditions and the possible presence of impurities. The consistency of the results and the general reliability of the procedures used was also checked in two ways. First, the stock concentration of the stock solutions of hydrogen peroxide, which were prepared from commercially available 30% hydrogen peroxide, was followed using iodometric titration. In a *ca.* 1 M stock solution, a gradual decrease in hydrogen peroxide concentration was observed. The overall decrease was 3.5% relative to the original concentration in 125 days, implying that decomposition because of the impurities present in the water used is probably not significant on the time scale of the initial rate studies (typically a few hours). Second, a test directly connected to the conditions of the initial rate measurements was also performed. Samples with hydrogen peroxide were prepared without a catalyst and in one case with phosphate-buffered $Fe(TPPS)^+$, where the porphyrin forms a catalytically inactive dimer. No measurable loss of hydrogen peroxide was detected in either case for 5–6 hours.

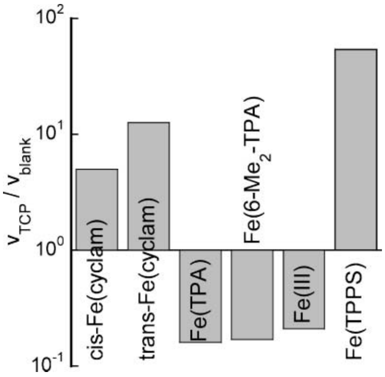

**Fig. 6** Initial rate ratios of $H_2O_2$ consumption in the presence ($v_{TCP}$, [TCP] = 1.0 mM) and absence ($v_{blank}$) of TCP. $T = 25.0$ °C. Note the logarithmic scale on the *y* axis.

### Mechanistic considerations

Two fundamentally different mechanisms can be envisioned for TCP oxidation in these systems. The first is when the catalyst basically catalyzes the decomposition of $H_2O_2$ and the reactive intermediates produced (*e.g.* hydroxyl radicals in Fenton-type reactions) cause the oxidative damage to the ligand.[36] In this case, the catalyst itself does not play a direct role in the oxidation of the substrate. The rate of $H_2O_2$ consumption should be similar in the presence and absence of an oxidizable substrate. However, the initial pH is about 2 units lower in the presence of TCP because of its acidity ($pK_a = 6.15$). Decomposition of hydrogen peroxide by Fenton-type catalysts is known to be slower in more acidic solutions.[37] Thus, the rate of $H_2O_2$ consumption can actually be lower in the presence of substrate. This general mechanism can finally result in a $H_2O_2$ consumption that is much larger than needed for the oxidation because the useful oxidation only happens after the first step of catalytic decomposition. This is clearly seen with $Fe^{3+}(aq)$ and $Fe(TPA)^{2+}$ from the $H_2O_2$ consumption results (Fig. 3). In the case of $Fe(6\text{-}Me_2\text{-}TPA)^{2+}$ the oxidation of the substrate is significantly less complete than with other catalysts (see Fig. 2), so catalytic decomposition may be a major source of $H_2O_2$ loss despite the relatively low overall oxidant consumption. It should also be explained at this point why $H_2O_2$ is present at the end of the oxidation process. The most likely reason is that the $H_2O_2$-decomposing activity of the catalysts is diminished by the increasing acidity and/or through complex formation with dicarboxylic acids formed as the final products of the oxidation.

A second possible mechanism is a catalytic cycle involving the catalyst, $H_2O_2$ and TCP. The substrate is oxidized in a direct reaction with an active high oxidation state iron complex. In this case, the catalytic cycle cannot operate without substrate and the rate of $H_2O_2$ consumption is clearly expected to be larger in the presence of substrate than in its absence. $Fe(TPPS)^+$ and the cyclam complexes seem to follow this pattern. They are inefficient catalysts of $H_2O_2$ decomposition as shown by the high ratios in Fig. 6. The actual catalytic cycle and the species participating in it may be different for the different catalysts and further studies are needed to identify them.

### Attempted use of methyltrioxorhenium(VII) as a catalyst

To obtain more general mechanistic information, an attempt to use methyltrioxorhenium (MTO, $CH_3ReO_3$), a well known and efficient activator for hydrogen peroxide,[41] to catalyze the oxidation of TCP was also made. The mechanisms of MTO-catalyzed oxidations are based on the formation of peroxo complexes $CH_3ReO_2(O\text{–}O)$, and $CH_3ReO(O\text{–}O)_2$, and it is understood that MTO activates $H_2O_2$ exclusively toward oxygen transfer.[41] Our results showed that MTO does not catalyze the oxidation of TCP or other chlorophenols by $H_2O_2$ at all. This was confirmed in both water and $CH_3CN$. In these experiments, only independently known and slow catalyst decomposition was observed and the chlorophenol was intact after a day. Thus it is concluded that oxygen transfer cannot be among the first steps of the oxidation of chlorophenols. This agrees with earlier mechanistic proposals, where phenoxyl radical formation through either hydrogen atom transfer or deprotonation of the phenol followed by electron transfer is the usual initial process.[6] The results presented here also have an important implication for future studies: the mechanistic conclusions drawn using the same catalysts for the epoxidation of olefins,[29–33] in which oxygen transfer is the most important step, are not necessarily valid for TCP oxidation.

## Conclusion

In this work, we defined quantitative and semi-quantitative measures of stoichiometric and kinetic efficiencies to characterize the catalytic oxidation of TCP. These definitions can be used for other similar oxidation systems as well. The overall stoichiometric efficiencies are similar for the six different catalysts used in this work, but kinetic observations clearly favor $Fe(TPPS)^+$. The results suggest that heme-like iron catalysts involving planar coordination of four nitrogen donor atoms may be the most successful ones to activate $H_2O_2$ toward chlorophenol oxidation. Light has an accelerating effect on the reaction.

## Experimental

### Materials

Commercial 2,4,6-trichlorophenol was purified by vacuum sublimation. Iron(III) *meso*-tetra(4-sulfonatophenyl) porphine chloride was purchased from Frontier Scientific (http://www.porphyrin.com). $Fe(NH_4)(SO_4)_2\cdot12H_2O$ was used as received. The complexes *cis*-[cyclamFeCl$_2$]Cl,[42] *trans*-[(cyclamFeCl$_2$)]BF$_4$,[42] [Fe(TPA)(CH$_3$CN)$_2$](ClO$_4$)$_2$,[30] and [Fe(6-Me$_2$-TPA)(CH$_3$CN)$_2$](ClO$_4$)$_2$[30] were prepared according to literature methods and characterized by $^1$H NMR and/or UV-vis spectroscopy. 2,4,6-Trichlorophenol-$d_2$ was prepared as described earlier.[35] $H_2O_2$ was determined by iodometric titration.[40] Ion exchanged and ultrafiltered water from a Millipore MILLI-Q purification system was used to prepare solutions.

### Instruments

A Shimadzu UV-3101PC scanning spectrophotometer and a Shimadzu TOC-5000A total organic carbon analyzer were used in this study. $^2$H NMR spectra were recorded in natural isotope distribution $H_2O$ and referenced to the signal of standard $CD_3CN$ ($\lambda$ = 1.55 ppm).[38,39] GC-MS experiments were performed on a Finnigan Magnum ion trap mass spectrometer equipped with a 30 m DB-5 column using He carrier gas. A Weiss Research CL3005 combination chloride ion selective electrode and a Hanna Instruments pH302 pH-meter were used. The electrode was calibrated every day using standard NaCl solutions. The lamp used in this study was a commercially available Regent 500 watt halogen lamp (Regent Lighting Corporation, Burlington, NC, USA).

## Acknowledgements

This research was supported by the Center for Catalysis, Institute for Physical Research and Technology, Iowa State University. Some experiments were conducted with the use of the facilities of the Ames Laboratory of the US Department of Energy, which is operated by Iowa State University of Science and Technology under contract W-7405-Eng-82. We acknowledge helpful discussions with Prof. W. S. Jenks and Mr. Youn-chul Oh. GL also wishes to thank the Fulbright Program and Hungarian funding agency OTKA (grant No. T042755) for financial support.

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# Green photochemistry: solar photooxygenations with medium concentrated sunlight

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***Received 14th September 2004, Accepted 18th November 2004***
***First published as an Advance Article on the web 3rd December 2004***
**DOI: 10.1039/b414230f**

The rose bengal sensitized photooxygenations of citronellol and 1,5-dihydroxynaphthalene were performed successfully under solar irradiation conditions, and complete conversions (>95%) were achieved in almost all cases in relatively short illumination times. The selected reactions were easily performed on multigram to kilogram scales using cheap and commercially available starting materials, and yielded important key-intermediates for industrial applications.

## Introduction

Over the last few decades, the growing demand for environmentally friendly technologies has led to an increasing interest in *Green Chemistry*.[1] Among the many *green chemical* approaches, photochemistry can serve as a valuable application since light is regarded as a *clean reagent*.[2] Despite obvious advantages in terms of selectivity and sustainability, photochemical applications for the production of chemicals on large industrial scales remained, however, rare.[3] To overcome this neglect, photochemical reactions have been recently subjected to moderately or highly concentrated sunlight,[4] and selected examples for the production of specific fine chemicals using modern solar collectors have been reported.[5]

## Results and discussion

All experiments were performed at the solar-chemical facility of the German Aerospace Center (DLR) close to Cologne, Germany (latitude 50°51′ N, 7°07′ E, 70 m above sea level).[6] The research site receives about 1500 hours of direct sunshine (with a peak in July/August) and about 850 kWh $m^{-2}$ of direct insolation per year, and thus provides sufficient conditions for solar-chemical operations. Two different sunlight-collecting systems were used for the present investigation.[7] The larger PROPHIS plant for multikilogram syntheses[8] and a smaller parabolic trough collector designed for laboratory-scale applications.[9] Both reactor types require direct sunlight since they can only concentrate the direct part of global radiation. The technical key-data of each reactor are given in Table 1.

Dye sensitized photooxygenations are superior model reactions for solar-chemical applications.[5,10] For the present study, we have selected rose bengal as a sensitizer since it shows a favorable absorption up to 600 nm with a maximum at 555 nm (data in ethanol).†[5b]

### Photooxygenation of citronellol

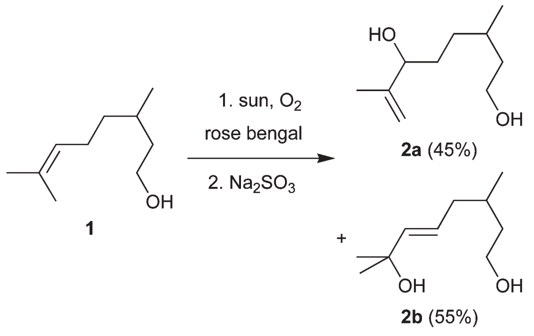
**Table 1** Technical data of the solar reactors[a]

| | PROPHIS | Small parabolic trough |
|---|---|---|
| Volume/l | 35–120 | 0.2–1 |
| CF[b]/suns | 32 | 15 |
| Aperture | | |
| Total/$m^2$ | 32 | 0.188 |
| Size per trough | 189 cm × 4.5 m | 20 cm × 94 cm |
| Troughs | 4 | 1 |
| Concentrator material | Ag (on glass) | DCG[c] (between glass) |
| Position to sun | 2 axis-tracking | Tracking (elevation)<br>Manual (azimuth) |
| System | Circulating | Circulating |

[a] At the location of the DLR in Cologne, Germany. [b] Geometric concentration factor; ratio of the collector aperture area to the absorber area. [c] Dichromated gelatine (Holotec GmbH, Germany); reflectivity range 550 ± 140 nm.

The photosensitized oxygenation (or Schenck-ene-reaction) of citronellol **1** was studied as a first example (Scheme 1).[11] This reaction is currently performed on a *ca.* 100 t $a^{-1}$ scale by Symrise (former Dragoco and Haarmann & Reimer) in Germany using artificial light sources.[11a] Further reduction and acid mediated cyclization of the regioisomer **2b** gives the important fragrance rose oxide, which makes this photoreaction a prototype for solar photochemical comparison studies.[12] For the 'outdoor' reactions in the PROPHIS loop (Table 2), the solvent methanol from the industrial process was replaced by the less hazardous isopropanol.

For the first experiment performed in August 1997, only one trough with an aperture of 8 $m^2$ was used. The reactor was loaded with a solution of 5.8 l (31.8 mol) of citronellol (**7**) and 20 g of rose bengal in 40 l of isopropanol. Upon illumination, the amount of citronellol was rapidly consumed and after *ca.*



**Scheme 1** Solar photooxygenation of citronellol **1**.

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**Table 2** Experimental data for the photooxygenation reactions of citronellol **1** using the PROPHIS loop

| | Experiment I | Experiment II |
|---|---|---|
| Date | 11.8.1997 | 12.9.2002 |
| Scale | | |
| Citronellol/l | 5.8 | 8.0 |
| Rose bengal/g | 20 | 36 |
| *i*-PrOH/l | 40 | 72 |
| $O_2$-flow/l h$^{-1}$ | 600 | 200 |
| Aperture/m$^2$ | 8 | 32 |
| Fluid flow/l min$^{-1}$ | 30 | 30 |
| Temperature/°C | 20 | 20 |
| Time (CEST) | 10:55–14:30 | 10:20–18:00 |
| Total (effective[a])/h | *ca.* 3 ½ (3) | *ca.* 7 ¾ (2 ¼) |
| Photons[b], (effective[c])/mol | 54.7 (47.1) | 442.6 (133.4) |
| Conversion[d] (%) | >95 | >95 |

[a] Time until conversion reaches an almost constant value. [b] Estimated amount of photons collected between 500–600 nm. [c] Estimated amount of photons (500–600 nm) for complete conversion. [d] Conversion of citronellol **1** as determined by GC-analysis (*vs.* tetradecane) after reduction with $Na_2SO_3$.

3 h, an almost quantitative conversion of **1** was already achieved. GC-analysis, performed after reduction of the corresponding sample with $Na_2SO_3$, furthermore proved the high purity of the regioisomeric photoproducts which were formed in a ratio of about 45 : 55 in favor of **2b** (determined *vs.* tetradecane as internal standard). The latter finding is in good agreement with the reported isolated yields of 35% (**2a**) and 60% (**2b**) from laboratory experiments with artificial light.[10b] During the experimental period the reactor collected 47.1 mol of photons in the important absorption range of rose bengal between 500–600 nm.‡

In the second run in September 2002, all 4 troughs were used, giving a total aperture of 32 m$^2$ (Fig. 1). In addition, the experiment was scaled-up to 8.0 l (43.9 mol) of citronellol (**1**) and 36 g of rose bengal in 72 l of isopropanol. The weather conditions were optimal and consequently, total conversion was readily observed after less than 3 h (Fig. 2). During this time, the PROPHIS plant received 133.4 mol of photons in the range of 500–600 nm—almost 3-times as much as during the experiment with only one trough.‡

Remarkably, the increase in aperture did not cause a better efficiency of the photooxygenation process. This becomes obvious when comparing the conversion based on time and area profiles for both experiments (Fig. 3). The main reason for this observation is the poor distribution of oxygen and thus the different saturation of it inside the reactor tubes, because the given technical set-up allows gas feeding only at the bottom of the first trough. Furthermore, the given feeding-nozzle generates relatively large gas bubbles with a small overall surface.

**Fig. 1** PROPHIS reactor during the photooxygenation of citronellol **1**.

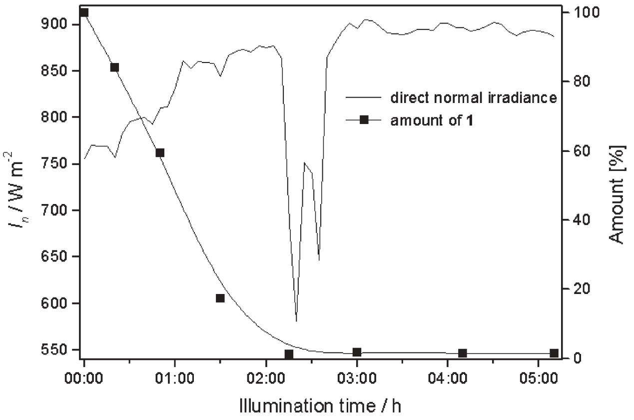


**Fig. 2** Direct normal irradiance and conversion *vs.* illumination time for the photooxygenation of citronellol **1** (Experiment II).

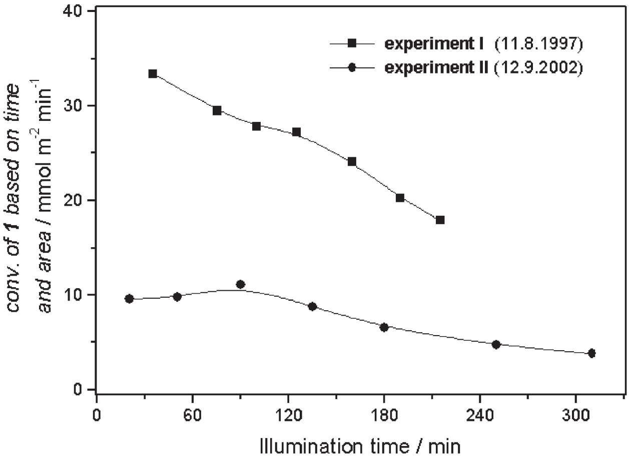
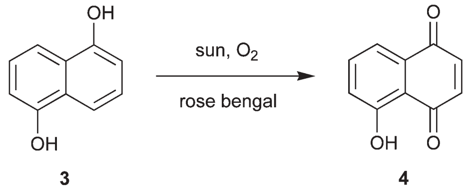


**Fig. 3** Conversion based on time and area *vs.* illumination time for both photooxygenations of citronellol **1**.

## Photooxygenation of 1,5-dihydronaphthalene

An additionally interesting application of the solar-chemical concept was the synthesis of the important intermediate Juglone (5-hydroxy-1,4-naphthoquinone, **4**)[13] from 1,5-dihydroxynaphthalene (Scheme 2). With artificial light sources, the photosensitized oxygenation of **3** furnishes Juglone in yields of



**Scheme 2** Solar photooxygenation of 1,5-dihydroxynaphthalene **3**.

70–75%, even on multigram scales.[14] Noteworthy, most of the thermal alternative pathways suffer from several disadvantages concerning yield, selectivity, sustainability or reproducibility.[15]

For the solar-chemical experiments, we have selected a small parabolic trough collector equipped with holographic mirrors (Table 1; Fig. 4). The given holographic concentrators (2 elements; 20 × 100 cm total) are especially designed to reduce warm-up effects (and thus the costs for process cooling) caused by infrared radiation and show a reflectivity range of 550 ± 140 nm—optimal for the usage of rose bengal.[9] Oxygen is added *via* a simple Y-connector which does not allow a constant oxygen flow or a homogeneous distribution of it within the absorber tube.

In August 2003, two laboratory-scale experiments were conducted using rose bengal as sensitizer and isopropanol as solvent. In contrast, the laboratory procedure commonly uses methylene blue and acetonitrile or a mixture of methanol with dichloromethane,[14] respectively. The experimental details and results from the solar-chemical studies are summarized in Table 3. In both cases, the progress of the reaction was followed *via* GC-analysis *vs.* tetradecane as internal standard.

The first test run was performed with 2.0 g of diol (**3**) and 0.1 g of rose bengal in 200 ml of solvent. The starting material was readily consumed and after 8 h, the conversion has already reached a constant value of 83%. During that period the reactor collected 7.4 mol of photons between 500–600 nm.‡ After work-up, the desired product (**4**) was obtained in 54% yield (65% based on conversion of **3**).

For the second experiment, the amount of diol (**3**) was reduced to 1.0 g in order to achieve complete conversion. After 3 h (Fig. 5), GC-analysis revealed that most of the starting diol (**3**) had already been consumed. At this stage the collector has received 2.3 mol of photons in the range of 500–600 nm.‡ After a total illumination period of *ca.* 9.5 h, Juglone was isolated in a compared to the laboratory experiments improved yield of 79%.

Although the photooxygenations of **3** required relatively long illumination times in comparison to the large scale experiments involving citronellol (**1**), it must be taken into account that solar-chemical experiments with non-concentrated sunlight often require several days or weeks to reach high conversion rates.[16] Additionally, the given laboratory-scale reactor and especially the oxygen feeding equipment were not optimized. Thus, the preliminary results obtained from the present study clearly indicate that the photosensitized oxygenation of 1,5-dihydroxynaphthalene (**3**)—especially if performed with the PROPHIS system—opens a promising and mild alternative pathway to Juglone (**4**).

**Table 3** Experimental data for the photooxygenation reactions of 1,5-dihydroxynaphthalene **3** using the laboratory-scale reactor

| | Experiment III | Experiment IV |
|---|---|---|
| Date | 4–5.8.2003 | 12–13.8.2003 |
| Scale | | |
| Diol **3**/g | 2.0 | 1.0 |
| Rose bengal/g | 0.1 | 0.1 |
| *i*-PrOH/ml | 200 | 200 |
| Aperture/m$^2$ | 0.188 | 0.188 |
| Fluid flow/l min$^{-1}$ | *ca.* 60 | *ca.* 60 |
| Temperature/°C | 20 | 20 |
| Time (CEST) | | |
| 1st day | 13:25–17:45 | 13:40–16:45 |
| 2nd day | 08:50–16:20 | 09:10–15:40 |
| Total (effective[a])/h | *ca.* 12 (8) | *ca.* 9 ½ (3) |
| Photons[b]/mol | | |
| 1st day | 4.3 | 2.3 |
| 2nd day | 6.3 | 4.2 |
| Total (effective[c])/mol | 10.5 (7.4) | 6.5 (2.3) |
| Conversion[d] (%) | 83 | >95 |
| Isolated yield[e] (%) | 54 (65[f]) | 79 |

[a] Time until conversion reaches an almost constant value. [b] Estimated amount of photons collected between 500–600 nm. [c] Estimated amount of photons (500–600 nm) for complete conversion. [d] Conversion of diol **3** as determined by GC-analysis (*vs.* tetradecane). [e] Isolated yield of Juglone **4**. [f] Yield calculated based on conversion.

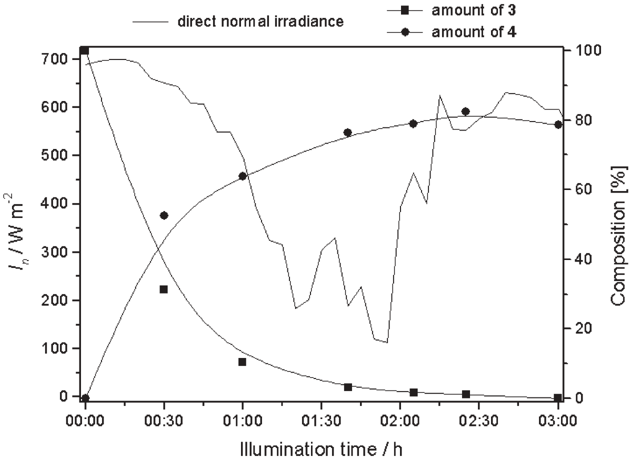


**Fig. 5** Direct normal irradiance and product composition *vs.* illumination time for the photooxygenation of 1,5-dihydroxynaphthalene **3** (Experiment IV).

**Fig. 4** Small scale parabolic trough reactor equipped with holographic mirrors during the solar photooxygenation of 1,5-dihydroxynaphthalene **3**.

## Conclusion

The present study on solar photooxygenations nicely demonstrates that the solar-chemical production of specific fine chemicals can serve as a powerful and environmentally friendly alternative to existing thermal processes. Cost estimates for specific fine chemicals (rose oxide[12] or ε-caprolactam[17]) furthermore revealed that an industrial solar-chemical production can indeed operate economically. Although not all conditions were optimal in the present study to realize Giacomo Ciamician's vision of the '*Photochemistry of the Future*',[18] a solar production plant in sunnier regions (*e.g.* in southern Spain) seems within range.

## Acknowledgements

This research project was financially supported by the *Arbeitsgemeinschaft Solar Nordrhein-Westfalen* (Themenfeld 3: Solare Chemie und Solare Materialuntersuchungen). The authors would like to thank Prof. Axel G. Griesbeck and Dr. Christian Sattler for their support, and Dr. Jens Bunte for help in the preparation of this manuscript.

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‡ The amounts of collected photons were calculated using *SEDES for Windows*.[19]

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# Room-temperature ionic liquids that dissolve carbohydrates in high concentrations

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*Received 19th August 2004, Accepted 15th October 2004*
*First published as an Advance Article on the web 26th November 2004*
**DOI: 10.1039/b412848f**

Carbohydrates are only sparingly soluble in common organic solvents as well as in weakly coordinating ionic liquids, such as [BMIm][BF$_4$]. Ionic liquids that contain the dicyanamide anion, in contrast, dissolve approx. 200 g L$^{-1}$ of glucose, sucrose, lactose and cyclodextrin. *Candida antarctica* lipase B mediated the esterification of sucrose with dodecanoic acid in [BMIm][dca].

## Introduction

There is considerable current interest in the utilization of carbohydrates as readily available, relatively inexpensive and renewable feedstocks for the chemical and related industries. Examples of the latter trend are sugar-derived biosurfactants[1] and esters of sugars with fatty acids.[2] The transformation of underivatised carbohydrates is still quite challenging due to their low solubility in almost any solvent but water. The few exceptions, such as DMF and DMSO, have many undesirable characteristics and are not compatible with many intended applications of carbohydrate-derived products.

Ionic liquids are currently the focus of increasing attention as reaction media for organic synthesis in general and enzymatic transformations in particular.[3] Their potential as media for carbohydrate transformations was first pointed out by us[4] and subsequently confirmed by Park and Kazkauskas[5] who described the lipase-catalysed acylation of glucose and maltose in ionic liquids. The best results were obtained in 1-methoxyethyl-3-methylimidazolium tetrafluoroborate, [M*O*EMIm][BF$_4$], which dissolved 5 g L$^{-1}$ of glucose at 55 °C.[5] More recently, the dissolution of high concentrations of α-cyclodextrin (350 g L$^{-1}$) in 1-methoxymethyl-3-methylimidazolium bromide has been reported.[6] 1-Butyl-3-methylimidazolium chloride passed the ultimate test as a solvent for carbohydrates by dissolving 100 g L$^{-1}$ of cellulose at 100 °C.[7]

MacFarlane and coworkers were the first to note that ionic liquids containing the dicyanamide (dca) anion dissolved glucose in high (>100 g L$^{-1}$) concentrations.[8,9] These ionic liquids were also able to dissolve di- and trisaccharides in considerable but unspecified amounts.[9,10]

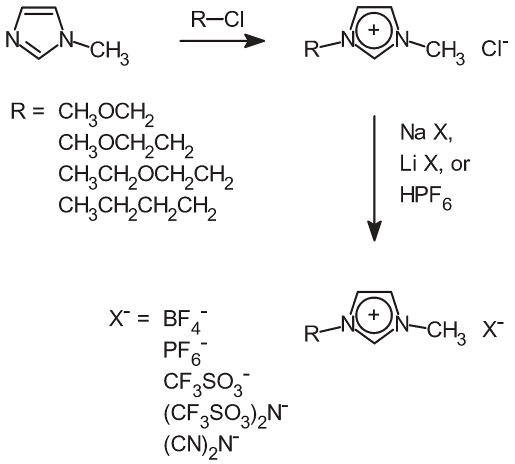
These observations prompted us to undertake a systematic study of the effects of the anion and substituents in the cation on the ability of dialkylimidazolium ionic liquids to dissolve mono-, di- and polysaccharides, the ultimate goal being their use as reaction media for performing (bio)catalytic transformations of industrially relevant carbohydrates. Herein we report our preliminary results in which we will show that certain room-temperature ionic liquids are able to dissolve high concentrations of carbohydrates and we will show that these solutions can be used for lipase-catalysed acylations.

## Results and discussion

The ionic liquids were synthesised according to slightly modified literature procedures[11] (see Scheme 1). Chloride ion may severely affect the properties of ionic liquids even in trace amounts.[12] Hence, it was removed *via* column chromatography,[5] which reduced the chloride contents from approx. 1% (w/w) in the crude ionic liquid to 200–300 ppm. Rigorous drying reduced the water contents to <500 ppm.

The solvatochromic shifts of the dca-containing ionic liquids were measured with Nile Red. The excitation energies ranged from 213–215 kJ mol$^{-1}$, which is well within the expected range and close to the value of the corresponding bis(trifluoromethylsulfonyl)imide compounds.[12,13] These results seem to confirm the notion that the solvatochromic shift of betaine dyes mainly depends on the nature of the cation.[14]

The solubility of β-D-glucose in the newly synthesised ionic liquids, as well as that in [BMIm][BF$_4$] and [BMIm][PF$_6$] was measured, using a spectrophotometric assay.[15] The solubilities of glucose in the various ionic liquids at 25 °C are shown in Table 1. Glucose dissolved in the ionic liquids to a much higher



**Scheme 1** Synthetic scheme.

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concentration than in *tert*-butyl alcohol and the expected positive effect of the oxygenated side-chains could indeed be observed (see Table 1). However, much to our surprise, the solubility of glucose was influenced much more by the nature of the anion than that of the cation. Ionic liquids containing the dicyanamide anion dissolved glucose more than an order of magnitude better than their tetrafluoroborate counterparts. MacFarlane and coworkers have asserted[9] that the high solubility of carbohydrates can be attributed to the H-bond acceptor properties of the dca anion, which was recently recognised as a prerequisite for dissolving complex molecules.[16] It would seem, in hindsight, that the high solubility of carbohydrates in [M*O*MMIm][Br] and [M*O*EMIm][Br][6] can probably be attributed to the bromide anion rather than the oxygenated imidazolium cation.[16] It came to us as a final surprise that [BMIm][dca] was a much better solvent for glucose than its oxygenated counterparts.

The solubility of glucose in these ionic liquids increased by a factor of 2.5–5 when the temperature was raised to 75 °C. Thus, [BMIm][dca] dissolved 211 and 405 g L$^{-1}$ at 40 and 75 °C, respectively.

The solubility of the disaccharide sucrose in [M*O*EMIm][[Tf$_2$N] and similar ionic liquids was much less than that of glucose, in spite of the oxygen atom in the side chain. The dca-containing ionic liquids, in contrast, dissolved sucrose even better than glucose, with [E*O*EMIm][dca] as a notable exception (Table 2). A further increase in solubility was observed when the temperature was raised to 60 °C.

The effort required to obtain these ionic liquids in a halide-free state prompted us to assess the influence of chloride ions on the solubility of sucrose in [BMIm][dca]. We found the effect to be small, as the solubility of sucrose (at 60 °C) increased from 282 g L$^{-1}$ to 294 g L$^{-1}$ in the presence of 1% of chloride.

As the use of ionic liquids as reaction media is our ultimate objective, we have investigated the acylation of sucrose by dodecanoic acid. Preliminary experiments showed that Novozym 435 catalysed the conversion of sucrose in [BMIm][dca] medium. Further work is in progress.

Additional experiments demonstrated the potential of [BMIm][dca] for dissolving carbohydrates (see Table 3). Lactose, which is extremely sparingly soluble in organic solvents, such as *tert*-butyl alcohol, dissolved readily. β-Cyclodextrin dissolved in [BMIm][dca] very slowly, but the final concentration was so high (see Table 3) that the mixture solidified upon cooling. Amylose, which is only sparingly (<0.5 g L$^{-1}$) soluble in water, dissolved in [BMIm][dca] to a final concentration of 4 g L$^{-1}$.

**Table 1** Solubility of β-D-glucose in ionic liquids at 25 °C

| Solvent | R | X | Solubility / g L$^{-1}$ |
|---|---|---|---|
| *tert*-Butyl alcohol | — | — | 0.3 |
| [BMIm][BF$_4$] | $C_4H_9$ | $BF_4$ | <0.5 |
| [BMIm][PF$_6$] | $C_4H_9$ | $PF_6$ | <0.5 |
| [M*O*MMIm][Tf$_2$N] | $CH_3OCH_2$ | $(CF_3SO_2)_2N$ | 0.5 |
| [M*O*MMIm][BF$_4$] | $CH_3OCH_2$ | $BF_4$ | 4.4 |
| [M*O*MMIm][TfO] | $CH_3OCH_2$ | $CF_3SO_3$ | 4.3 |
| [M*O*EMIm][Tf$_2$N] | $CH_3OCH_2CH_2$ | $(CF_3SO_2)_2N$ | 0.5 |
| [M*O*EMIm][PF$_6$] | $CH_3OCH_2CH_2$ | $PF_6$ | 2.5 |
| [M*O*EMIm][BF$_4$] | $CH_3OCH_2CH_2$ | $BF_4$ | 2.8 |
| [M*O*EMIm][TfO] | $CH_3OCH_2CH_2$ | $CF_3SO_3$ | 3.2 |
| [E*O*EMIm][Tf$_2$N] | $C_2H_5OCH_2CH_2$ | $(CF_3SO_2)_2N$ | 0.5 |
| [E*O*EMIm][PF$_6$] | $C_2H_5OCH_2CH_2$ | $PF_6$ | 0.7 |
| [E*O*EMIm][BF$_4$] | $C_2H_5OCH_2CH_2$ | $BF_4$ | 2.8 |
| [M*O*MMIm][dca] | $CH_3OCH_2$ | $(CN)_2N$ | 66 |
| [M*O*EMIm][dca] | $CH_3OCH_2CH_2$ | $(CN)_2N$ | 91 |
| [E*O*EMIm][dca] | $C_2H_5OCH_2CH_2$ | $(CN)_2N$ | 70 |
| [BMIm][dca] | $C_4H_9$ | $(CN)_2N$ | 145 |

**Table 2** Solubility of sucrose in ionic liquids

| | Solubility / g L$^{-1}$ | |
|---|---|---|
| Solvent | 25 °C | 60 °C |
| [M*O*EMIm][Tf$_2$N] | 0.13 | |
| [M*O*EMIm][BF$_4$] | 0.4 | |
| [M*O*EMIm][PF$_6$] | 0.7 | |
| [M*O*EMIm][TfO] | 2.1 | |
| [M*O*MMIm][dca] | 249 | 352 |
| [M*O*EMIm][dca] | 220 | |
| [E*O*EMIm][dca] | 50 | 240 |
| [BMIm][dca] | 195 | 282 |
| *tert*-Butyl alcohol | | 0.5[a] |

[a] From ref. 15.

**Table 3** Solubility of di- and polysaccharides in [BMIm][dca]

| | Solubility / g L$^{-1}$ | | |
|---|---|---|---|
| Sugar | 25 °C | 60 °C | 75 °C |
| Sucrose | 195 | 282 | |
| Lactose | 51 | | 225 |
| β-Cyclodextrin | | | 750 |
| Amylose | 4 | | |

In conclusion, we have shown that ionic liquids based on the dicyanamide anion are highly effective, non-protic solvents that dissolve carbohydrates from glucose to starch and even cellulose in large amounts. We have furthermore shown that enzymatic acylation with a fatty acid takes place in such a medium. Investigations are underway to ascertain the scope of carbohydrate conversions in dca ionic liquids, including ones containing other classes of cations.

## Experimental

### Materials

All chemicals were purchased from Aldrich. Novozym 435 was received from Novozymes (Bagsvaerd, Denmark) as a gift.

### Instruments

NMR spectra were measured on a Varian VXR400 spectrometer. UV measurements were performed on a Cary 3 spectrometer. Chloride contents were measured on a Dionex DX-120 instrument.

### Synthesis of ionic liquids

All ionic liquids were dried under vacuum over $P_2O_5$ until the water contents were <500 ppm according to Karl Fischer titration.

**[M*O*MMIm][Cl]**. Chloromethyl methylether (30 mL, 0.4 mol **CAUTION:** carcinogenic) was added dropwise to 1-methylimidazole (32 mL, 0.4 mol) under stirring at 0 °C, then kept at

50 °C for 1 h. The mixture was cooled to room temperature and washed three times with 70 mL ethyl acetate. After removal of the solvent by rotary evaporation the residual liquid solidified at room temperature (61.4 g, 95%), mp 66–68 °C.

**[M*O*MMIm][Tf$_2$N]**. To a solution of [M*O*MMIm][Cl] (6 g, 36.9 mmol) in acetone (40 mL) was added LiN(Tf)$_2$ (14.6 g, 5.1 mmol) and the mixture was stirred for 3 h. The acetone was removed by rotary evaporation and dichloromethane (40 mL) was added. The resulting mixture was stirred overnight, brought on a silica gel column and eluted with dichloromethane. The eluate was twice washed with water (40 mL), dried over anhydrous magnesium sulfate and concentrated by rotary evaporation (12.2 g, 81%).

**[MOMMIm][PF$_6$]**. A 60% aqueous solution of HPF$_6$ (17.5 mL, 0.13 mol) was slowly added dropwise to a stirred solution of [M*O*MMIm][Cl] (16.2 g, 0.1 mol) in water (50 mL) at 0 °C. Subsequently the mixture was stirred at room temperature for 12 h, the solids were obtained by filtration, washed two times with water (50 mL) and dried under vacuum (21.2 g, 80%), mp 67–69 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ = 9.18 (s, 1H), 7.85 (d, 1H), 7.80 (d, 1H), 5.69 (s, 2H), 4.12 (s, 3H), 3.46 (s, 3H). IR (KBr): 3179, 3128, 2963, 2942, 1582, 1563, 832 cm$^{-1}$.

**[M*O*MMIm][BF$_4$]**. To a solution of [M*O*MMIm][Cl] (16.2 g, 0.1 mol) in acetone (40 mL) was added NaBF$_4$ (13.2 g, 0.12 mol). The mixture was stirred for 48 h, the solid NaCl was removed by filtration and the filtrate was concentrated. The residual oil (22.1 g) was brought on a silica gel column and eluted with acetone–chloroform (50 : 50, v/v). The eluate was concentrated by rotary evaporation; the residue was dissolved in dichloromethane (50 mL), washed twice with saturated aqueous sodium carbonate solution (50 mL), dried over anhydrous magnesium sulfate and concentrated under vacuum (18.4 g, 86%). $^1$H NMR (acetone-$d_6$): $\delta$ = 9.03 (s, 1H), 7.77 (d, 1H), 7.72 (d, 1H), 5.62 (s, 2H), 4.05 (s, 3H), 3.42 (s, 3H). IR (film): 3163, 3119, 2957, 2840, 1580, 1561, 1063 cm$^{-1}$.

**[M*O*MMIm][Tf]**. To a solution of [M*O*MMIm][Cl] (6.0 g, 36.9 mmol) in 20 mL acetone was added NaCF$_3$SO$_3$ (6.35 g, 36.9 mmol). The resulting mixture was stirred for 24 h, the solid NaCl was removed by filtration, the filtrate was brought on a silica gel column and eluted with acetone. The eluate was concentrated by rotary evaporation (8.3 g, 81.4%).

**[M*O*MMIm][dca]**. To a solution of [M*O*MMIm][Cl] (9.4 g, 57.7 mmol) in 50 mL acetone was added NaN(CN)$_2$ (5.2 g, 57.7 mmol). The mixture was stirred for 24 h and the solid NaCl was removed by filtration. The filtrate was brought on a silica gel column and eluted with acetone. The eluate was concentrated by rotary evaporation (7.6 g, 83.8%). $^1$H NMR (acetone-$d_6$): $\delta$ = 9.27 (s, 1H), 7.84 (m, 1H), 7.79 (m, 1H), 5.67 (s, 2H), 4.10 (s, 3H), 3.42 (s, 3H). MS (esp$^-$): *m*/*z* 66.2 (100%, dca$^-$).

**[M*O*EMIm][Cl]**. 2-Chloroethyl methyl ether (36.5 mL, 0.4 mol) was added to 1-methylimidazole (32 mL, 0.4 mol) under stirring. After 48 h at 80 °C the mixture was cooled to room temperature, washed three times with ethyl acetate (70 mL) and concentrated by rotary evaporation. The residual yellow oil solidified at room temperature (64 g, 92%), mp 65–68 °C.

**[M*O*EMIm][Tf$_2$N]** was synthesised from [M*O*EMIm][Cl] and LiN(Tf)$_2$ as described for [M*O*MMIm][Tf$_2$N] (79%).

**[M*O*EMIm][PF$_6$]** was synthesised from [M*O*EMIm][Cl] and HPF$_6$ as described for [M*O*MMIm][PF$_6$] (30.5%). $^1$H NMR (acetone-$d_6$): $\delta$ = 8.90 (s, 1H), 7.69 (d, 1H), 7.65 (d, 1H), 4.51 (t, 2H), 4.04 (s, 3H), 3.81 (t, 2H), 3.44 (s, 3H). IR (film): 3172, 3126, 2943, 2903, 2840, 1576, 1454, 824 cm$^{-1}$.

**[M*O*EMIm][BF$_4$]** was synthesised from [M*O*EMIm][Cl] and NaBF$_4$ as described for [M*O*MMIm][BF$_4$] (49.3%). $^1$H NMR (acetone-$d_6$): $\delta$ = 8.88 (s, 1H), 7.68 (d, 1H), 7.65 (d, 1H), 4.48 (t, 2H), 4.01 (s, 3H), 3.79 (t, 2H), 3.34 (s, 3H). IR (film): 3164, 3123, 2932, 1576, 1455, 1058 cm$^{-1}$.

**[M*O*EMIm][TfO]** was synthesised from [M*O*EMIm][Cl] and NaCF$_3$SO$_3$ as described for [M*O*MMIm][Tf] (81%).

**[M*O*EMIm][dca]** was prepared from [M*O*EMIm][Cl] and NaN(CN)$_2$ as described for [M*O*MMIm][dca] (83%). $^1$H NMR (acetone-$d_6$): $\delta$ = 9.08 (s, 1H), 7.75 (m, 1H), 7.72 (m, 1H), 4.54 (t, 2H), 4.07 (s, 3H), 3.83 (m, 3H). MS (esp$^-$): *m*/*z* 66.2 (100%, dca$^-$).

**[E*O*EMIm][Cl]**. 2-Chloroethyl ethylether (44 mL, 0.4 mol) was added to 1-methylimidazole (32 mL, 0.4 mol) while stirring. After 48 h at 100 °C the mixture was cooled to room temperature and washed three times with ethyl acetate (70 mL). Removal of the solvent by rotary evaporation afforded a brown oil (69.0 g, 90.6%).

**[E*O*EMIm][Tf$_2$N]** was prepared from [E*O*EMIm][Cl] and LiN(Tf)$_2$ as described for [M*O*MMIm][Tf$_2$N] (91%).

**[E*O*EMIm][PF$_6$]**. A 60% aqueous solution of HPF$_6$ (17.5 mL, 0.13 mol) was slowly added dropwise to a stirred solution of [E*O*EMIm][Cl] (20.0 g, 0.1 mol) in water (50 mL) at 0 °C. After 12 h at room temperature, the ionic liquid bottom layer was separated, washed twice with water (50 mL) and with aqueous saturated sodium carbonate solution (50 mL). Purification according to literature method B (ref. 5) afforded a yellow oil (25.6%). $^1$H NMR (acetone-$d_6$): $\delta$ = 8.89 (s, 1H), 7.69 (d, 1H), 7.65 (d, 1H), 4.50 (t, 2H), 4.04 (s, 3H), 3.84 (t, 2H), 3.56 (q, 2H), 1.16 (t, 3H). IR(film): 3171, 3125, 2979, 2936, 2877, 1575, 1451, 841 cm$^{-1}$.

**[E*O*EMIm][BF$_4$]** was synthesised from [E*O*EMIm][Cl] and NaBF$_4$ as described for [M*O*MMIm][BF$_4$]. Purification according to method B (ref. 5) afforded a yellow oil (35.5%). $^1$H NMR (acetone-$d_6$): $\delta$ = 8.90 (s, 1H), 7.69 (d, 1H), 7.66 (d, 1H), 4.48 (t, 2H), 4.02 (s, 3H), 3.84 (t, 2H), 3.55 (q, 2H), 1.2 (t, 3H). IR (film): 3163, 3123, 2977, 2933, 2874, 1575, 1453, 1059 cm$^{-1}$.

**[E*O*EMIm][TfO]** was synthesised from [E*O*EMIm][Cl] and NaCF$_3$SO$_3$ as described for [M*O*MMIm][TfO] (90.6%).

**[E*O*EMIm][dca]** was obtained from [E*O*EMIm][Cl] and NaN(CN)$_2$ as described for [M*O*MMIm][dca] as a yellow oil (90.1%). $^1$H NMR (acetone-$d_6$): $\delta$ = 9.09 (s, 1H), 7.76 (d, 1H), 7.72 (d, 1H), 4.54 (t, 2H), 4.07 (s, 3H), 3.87 (m, 2H), 3.57 (m, 2H), 1.16 (t, 3H). MS (esp$^-$): *m*/*z* 66.2 (100%, dca$^-$).

**[BMIm][dca]**. To a solution of [BMIMm][Cl] (8.7 g, 5 mmol) in acetone (20 mL) was added NaN(CN)$_2$ (4.45 g, 5 mmol); the mixture was stirred for 24 h and the solid NaCl was removed by filtration. The filtrate was brought on a silica gel column and eluted with dichloromethane–acetone (30 : 70, v/v). The eluate was concentrated by rotary evaporation (8.5 g, 83.3%). $^1$H NMR (acetone-$d_6$): $\delta$ = 9.13 (s, 1H), 7.80 (m, 1H), 7.73

(m, 1H), 4.39 (t, 2H), 4.07 (s, 3H), 1.95 (m, 2H), 1.42 (m, 2H), 0.976 (t, 3H). MS (esp$^-$): *m*/*z* 66.2 (100%, dca$^-$).

### Solvatochromic shift measurements

Nile Red (0.4 mg) was dissolved in the ionic liquid (0.5 mL) and $\lambda_{max}$ (in nm) was measured at 25 °C. The molar transition energy ($E_{NR}$ in kJ mol$^{-1}$) was calculated from:

$$E_{NR} = 1196251/\lambda_{max}$$

where $1196251 = hcN_A \times 10^6$.

### Enzymatic esterification of sucrose

Sucrose (0.5 g, 1.46 mmol), dodecanoic acid (0.585 g, 3.0 mmol), immobilised *Candida antarctica* lipase (Novozym 435, 100 mg) and activated molecular sieve A4 were mixed with 8 mL [BMIm][dca] and stirred at 55 °C. Samples were taken and analysed by TLC. The product was identified by comparison with an authentic sample.

## Acknowledgements

A donation of Novozym 435 by Novozymes (Bagsvaerd, Denmark) is gratefully acknowledged. Q.L. thanks the CSC for financial support.

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# Microwave-promoted synthesis of β-hydroxy sulfides and β-hydroxy sulfoxides in water

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*Received 9th September 2004, Accepted 18th November 2004*
*First published as an Advance Article on the web 3rd December 2004*
**DOI: 10.1039/b413811b**

A simple, efficient and environmentally friendly one-pot synthesis of β-hydroxy sulfoxides in water under microwave irradiation is reported.

## Introduction

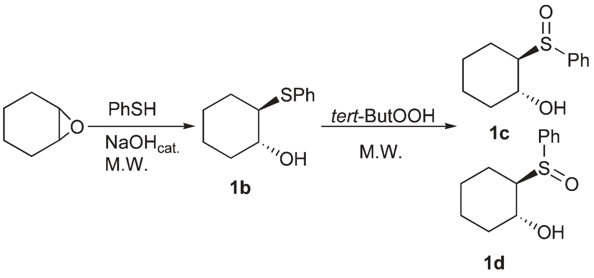
β-Hydroxy sulfides and β-hydroxy sulfoxides are important intermediates in organic synthesis.[1]

The former are versatile building blocks for synthesizing cyclic sulfides,[2] allylic alcohols,[1] benzoxathiepines,[3] benzothiazepines[4] and thioketones.[5] On the other hand the readily accessible β-hydroxy sulfoxides have an extended use in asymmetric synthesis.[6] They find also a useful application in the preparation of naturally occurring compounds such as leukotrienes.[7]

The most important synthetic route to β-hydroxy sulfide is the ring opening of epoxides with thiolates.[7] It can be promoted by acids, Lewis catalyst or metal salts.[8] Thiolysis in water was investigated for the first time by Fringuelli and coworkers,[9] where the formation of β-hydroxy sulfides was promoted by Lewis acids such as $InCl_3$[9] and $ZnCl_2$.[10]

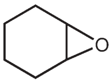
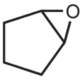
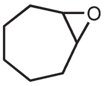
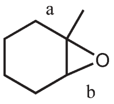
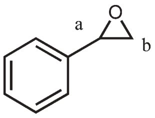
β-Hydroxy sulfoxides are commonly prepared by oxidation of β-hydroxy sulfides with conventional oxidizing agents.

We herein report the optimization of a one-pot protocol for the preparation of β-hydroxy sulfoxides in water, promoted by microwave irradiation. The opening of the epoxide and the subsequent sulfoxidation were accelerated by microwave and the desired product was obtained in only 15 minutes with very good yield. (Scheme 1) (see Table 1). Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions with short reaction times and in high yield and regioselectivity.[11] Indeed microwave dielectric heating in a pressurized system rapidly increases temperature far above the boiling point of the solvent and leads to a uniform energy transfer to the reactants of the chemical reaction.



**Scheme 1** Example of one-pot synthesis.

**Table 1** Thiolysis by thiophenol of epoxides (**1a–6a**) in water to give β-hydroxy sulfides

| Entry | Epoxide | $T$/°C | Time/ min | Power/ Watt | Yield (%) | a/b[a] |
|---|---|---|---|---|---|---|
| 1 |  **1a** | 25 | 240 | — | 80 | |
| 2 | **1a** | 150 | 5 | 400 | 97 | |
| 3 | **1a** | 110 | 5 | — | 30 | |
| 4 |  **2a** | 25 | 300 | — | 72 | |
| 5 | **2a** | 150 | 5 | 400 | 95 | |
| 6 |  **3a** | 25 | 1440 | — | 43 | |
| 7 | **3a** | 150 | 10 | 400 | 91 | |
| 8 |  **4a** | 25 | 300 | — | 77 | 5/95 |
| 9 | **4a** | 150 | 5 | 400 | 85 | 3/97 |
| 10 |  **5a** | 25 | 270 | — | 72 | 80/20 |
| 11 | **5a** | 150 | 5 | 400 | 88 | 65/35 |
| 12 |  **6a** | 25 | 180 | — | 85 | 5/95 |
| 13 | **6a** | 150 | 5 | 400 | 98 | 3/97 |

[a] Refers to the ratio of a-carbon and b-carbon, determined by $^1$H-NMR and HPLC analyses.

Water is cheap, readily available and nontoxic resulting in an economic process and has clear advantages as an environmentally friendly solvent alternative in organic synthesis. The heating effect utilized in microwave-assisted organic transformations is due to the dielectric constant of the solvent. For this

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**Table 2** Optimization of one pot protocol using **1a** and thiophenol

| Entry | *tert*-ButOOH/mol equiv.$^{-1}$ | $T$/°C | Time/min | Power/Watt | **1c** : **1d** | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 3.0 | 25 | 720 | — | 35 : 65 | 60 |
| 2 | 3.0 | 70 | 330 | — | 30 : 70 | 65 |
| 3 | 1.0 | 70 | 10 | 400 | 29 : 71 | 34 |
| 4 | 1.0 | 70 | 15 | 400 | 31 : 69 | 43 |
| 6 | 2.0 | 100 | 15 | 400 | 25 : 75 | 89 |

reason, water is therefore a very useful solvent for microwave-assisted organic synthesis.[11]

## Results and discussion

The reaction was performed with a laboratory microwave oven in a sealed tube controlled at 150 °C with an optical fiber in the presence of a catalytic amount of sodium hydroxide[12] (1.5%). The epoxide and the sulfide were used in a stoichiometric ratio. The β-hydroxy sulfide was obtained in quantitative yields (for reaction conditions see Table 1). In the one-pot procedure *tert*-butyl hydroperoxide (2.0 equiv.) was added to the same reaction media at 100 °C leading to β-hydroxy sulfoxides **1c** and **1d** in very good yields. No appreciable amounts of the corresponding sulfone were found.

This reaction was optimized using epoxide **1a** as starting material and thiophenol. Different parameters such as temperature, equivalent of oxidant and reaction time were studied (see Table 2). The β-hydroxy sulfoxides were isolated in 89% yield as a 25 : 75 mixture of diastereoisomers **1c** and **1d** of known configuration[1,9] (see Scheme 1).

In order to extend our protocol we have also investigated the thiolysis of a variety of epoxides (**1a–6a**) with thiophenol.

When the thiolysis was performed with microwave irradiation the reaction was very rapid and the products isolated from the reaction media were pure and did not need further purification.

At room temperature and in the absence of microwave irradiation the reaction times were in the range of 3–24 hours and the yields were lower (Table 1).

The rate acceleration observed can be justified as a consequence of the higher temperature and of the microwave irradiation. The opening of **1a** performed with conventional heating at 110 °C provided the expected product **1b** with only 30% yield (see Table 1 entry 3).

In all cases the ring opening was completely *anti*-stereoselective and the only products obtained were the *trans*-β-hydroxy sulfides.[13] The reaction proceeded *via* an $S_N2$ mechanism with attack of the thiol at the less substituted b-carbon, except for compound **5a** where the attack was driven predominantly at the benzylic a-carbon by an electronic effect.

## Conclusion

In conclusion we have demonstrated that the thiolysis of several epoxides in water, under controlled microwave irradiation, can be performed in a short time and with quantitative yield without the use of any metal catalyst. By coupling this procedure with the *in situ* oxidation of sulfide mediated by *tert*-butyl hydroperoxide, we have optimized a one-pot procedure for the preparation of β-hydroxy sulfoxides.

## Experimental

### Typical procedure of opening of an epoxide 1a–6a in the presence of thiophenol

Thiophenol (1.5 mmol) and epoxide (1.5 mmol) were suspended in water (3 ml), then sodium hydroxide (0.022 mmol) was added . The reaction tube (25 ml) was sealed with a Teflon® cap and irradiated in the cavity of a multimode Milestone MicroSYNTH labstation for the appropriate time at 150 °C, using an irradiation power of 400 Watt. The tube was cooled to 50 °C by gas-jet cooling. The reaction mixture was extracted with diethyl ether (3 × 5 ml). The combined organic layers were dried on magnesium sulfate and removed under reduced pressure to give pure product.

### Optimized procedure for one-pot synthesis of β-hydroxy sulfoxide

Thiophenol (1.5 mmol.) and epoxycyclohexane (1.5 mmol) were suspended in water then sodium hydroxide was added (0.022 mmol). The reaction tube was sealed with a Teflon® cap and irradiated in the cavity of a microwave apparatus at 150 °C for 5 minutes. The reaction tube was cooled to room temperature by gas-jet cooling, *tert*-ButOOH (3.0 mmol) was added and then irradiated in the cavity of microwave apparatus at 100 °C using an irradiation power of 400 Watt. After the appropriate reaction time the tube was cooled to 50 °C by gas-jet cooling. The reaction mixture was extracted with diethyl ether (3 × 5 ml). The combined organic layers were dried on magnesium sulfate and the solvent was removed under reduced pressure to give the β-hydroxy sulfoxides as a mixture of diastereoisomers.

## Acknowledgements

This work was supported by a PRIN project of the Italian MIUR. We want to thank Dr. Giorgio Abbiati and Dr.ssa Alessandra Bellinazzi for their help with the microwave apparatus.

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13 The *trans* configuration was deduced from the $J_{\text{H–H}}$ coupling constants: for more information see ref. 1.

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