Green Chemistry

Cutting-edge research for a greener sustainable future

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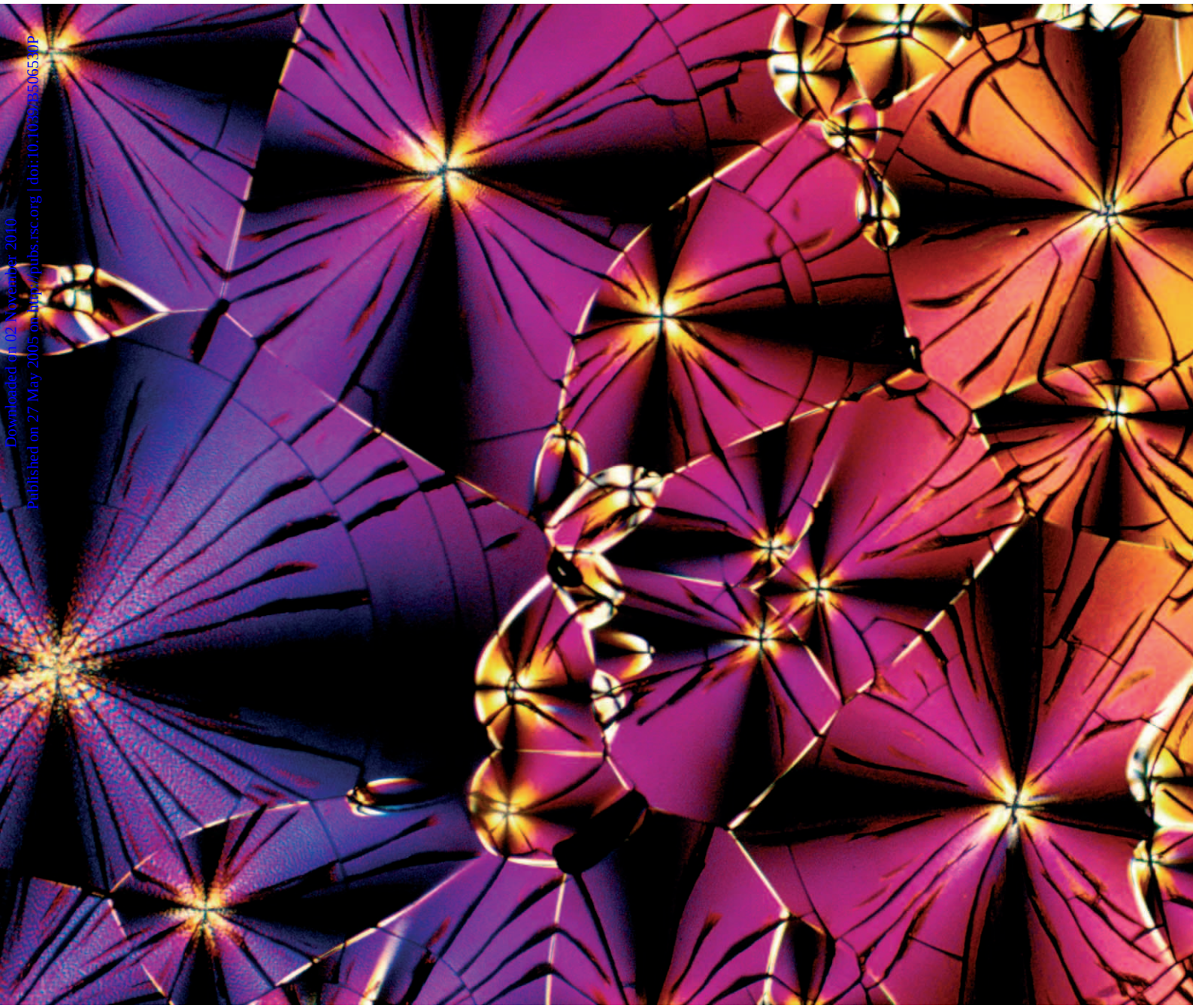

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Polarized light micrograph revealing the spherulitic composition and interference colours of a thin melt preparation of biotin crystallites.
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HIGHLIGHT

Highlights

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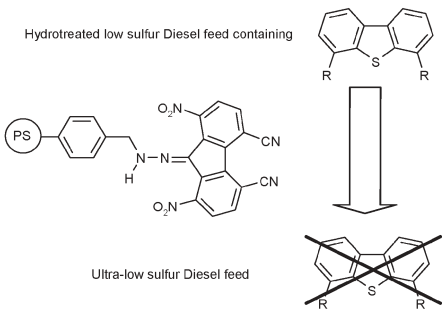

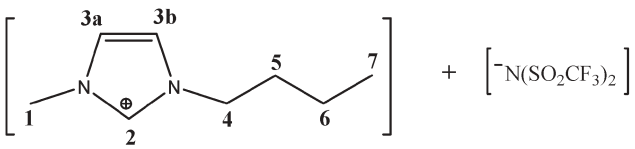

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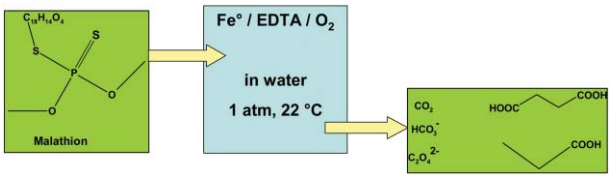

Detoxification of malathion a chemical warfare agent analog using oxygen activation at room temperature and pressure

Christina E. Noradoun, Chongkham S. Mekmaysy, Ryan M. Hutcheson and I. Francis Cheng*

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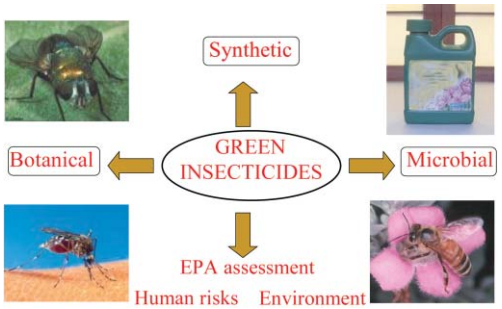

New trends in pest control: the search for greener insecticides

Óscar López,* José G. Fernández-Bolaños and María Victoria Gil

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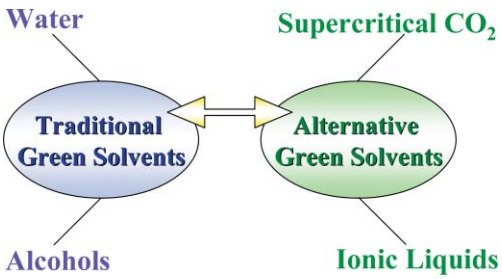

Liquid–liquid behaviour of ionic liquid–1-butanol–water and high pressure CO_2-induced phase changes

Vesna Najdanovic-Visak, Luís P. N. Rebelo and Manuel Nunes da Ponte*

This work aims at contributing to the design of new environmentally benign extractive technologies for green chemistry, which use traditional and alternative, clean solvents.

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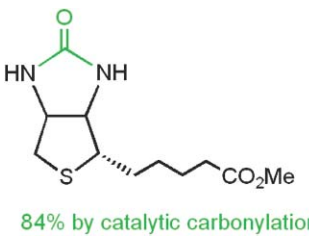
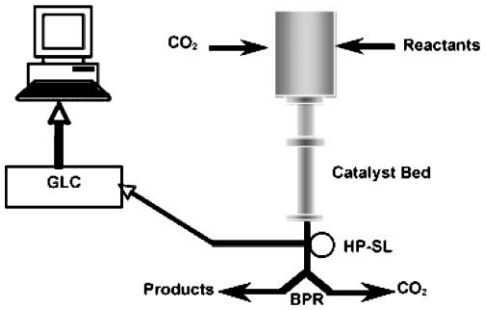
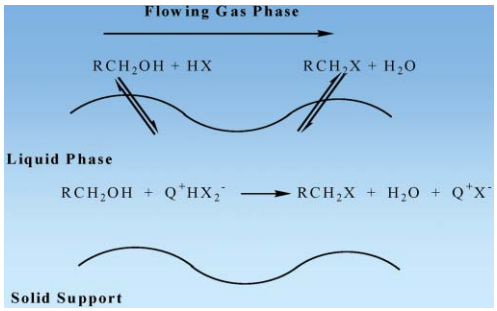


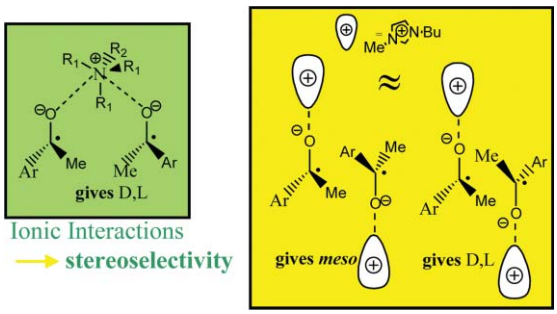
Preparation of biotin derivatives by catalytic oxidative carbonylation of diamines

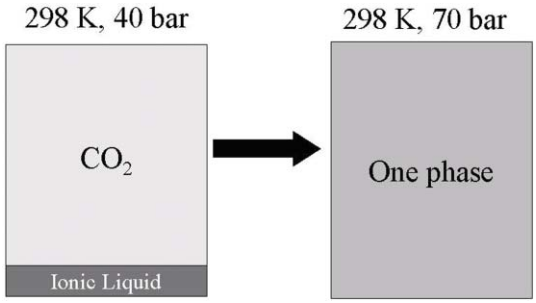
Yue Zhang, Kara Forinash, Courtney R. Phillips and Lisa McElwee-White*

Biotin methyl ester can be synthesized using catalytic carbonylation to generate the urea, avoiding the traditional phosgene and phosgene derivative methodology.









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The first Green Chemistry workshop in Ethiopia

Peter Licence[a] and Nigist Asfaw[b]

DOI: 10.1039/b501367b

Introduction

The first Green Chemistry workshop in Ethiopia was organized jointly by the Schools of Chemistry at both Addis Ababa University (AAU) and the University of Nottingham (UoN) in association with the Chemical Society of Ethiopia (CSE).

The primary objective of the workshop was to create awareness among both students and professionals in the industrial and academic sectors of the Ethiopian scientific community. A second and more fundamental objective was the sensitization of policy makers to the scientific grounding of both environmental sustainability and Green Chemistry and its subsequent support through its introduction into the academic curriculum throughout the region. The organizing committee is satisfied that the first steps towards achieving these goals have been successful.

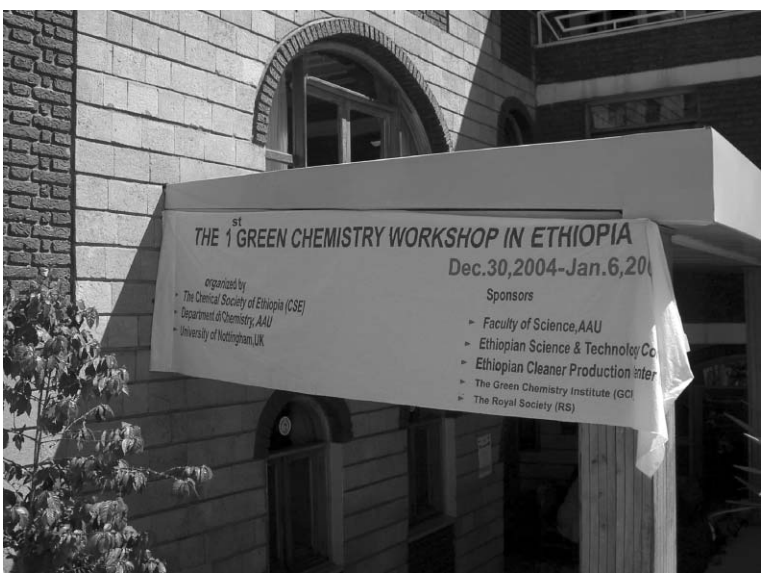
Report

The workshop was held at Ras Amba Hotel, Addis Ababa between December 30th 2004 and January 6th 2005 and was attended by a total of approximately 120 delegates drawn from all sectors of the Ethiopian scientific community. Atto Mulugeta Amha, the Commissioner of the Ethiopian Science and Technology Commission, officially opened the workshop and made a number of pungent comments about sustainable development with particular reference to economic development within the region.

The first sessions of the workshop were devoted to high school participants. One female and one male student accompanied by their chemistry teacher were invited from 20 high schools located in the Greater Addis area. These sessions were a resounding success and all delegates participated in a very lively scientific debate about existing governmental policies in both Ethiopia and Western nations.

The second section of the workshop was aimed at increasing the awareness of environmental problems associated with existing industrial processes. Attendees came from fifteen manufacturing enterprises (leather, chemicals, printing, tannery, sugar, food, beverages, detergent, textiles and cement enterprises), in total 30 representatives were present. An introductory lecture was followed by a lecture on key issues surrounding Green Chemistry, *i.e.* sustainability, chemical accidents, minimization of inherent risks *etc*. The discussion session centered on how to implement Green Chemistry in existing industries in Ethiopia, where over 90% of effluents are discharged directly to the environment without proper treatment.

The final sessions of the event were aimed at the academic establishment and attracted a large number of participants from universities throughout Ethiopia. In addition, participants were also invited from research institutions including the International Livestock Research Institute (ILRI), the Ethiopian Science Technology Commission (ESTC), the Ethiopian Cleaner Production Centre (ECPC) and the US Environmental Protection Agency (EPA). An introductory lecture highlighting the concepts of Green Chemistry, including the twelve principles of Green Chemistry with particular emphasis on the incorporation of "green pedagogy" into existing courses was delivered. For Green Chemistry to enter widespread practice, chemists must be educated about Green Chemistry during their academic and professional training. Educational materials used in the teaching of Green Chemistry including suggested lab manuals, posters and a CD with copies of all lectures was distributed to all participants. The discussion session was lively and filled with enthusiasm. Commitment to the inclusion of Green Chemistry into both undergraduate and postgraduate programs was a common theme. As a side comment, the forum also proved an excellent meeting point for people working in different establishments. A number of ideas were developed by the delegates to increase the amount of inter-departmental collaboration in general.



General remarks and comments

One important question that was raised by the participants during the discussion part of the three different sessions was: "Will Green Chemistry be sustainable in Ethiopia?" After a thorough discussion and exchange of ideas, the participants agreed that the program initiated should continue and all the participants of the workshop, and other concerned individuals and institutions should work together to promote Green Chemistry throughout the region. Participants were assured that such events would continue and that the organizers would continue to promote and popularize Green Chemistry in Ethiopia.

In addition to the organized workshops, additional lectures were given to the science faculty of Addis Ababa University, the chemistry department of Gonder University and the International Livestock Research Institute (ILRI) in Addis Ababa. Unfortunately, a formal lecture at the University of Bahir Dar had to be postponed because of a delayed flight, however, productive discussions were held with faculty members who were just as enthusiastic as their Addis colleagues.

Organizing committee

Dr Nigist Asfaw, Department of Chemistry, AAU

Dr Yonas Chebude, Department of Chemistry, AAU, Executive member of CSE

Dr Feleke Zewge, Department of Chemistry, AAU, Executive member of CSE

Lecturers

Dr Peter Licence, School of Chemistry, University of Nottingham, UK

Dr Egid Mubofu, Chemistry Department, University of Dar es Salaam, Tanzania

Mr Simon Poliakoff, VSO in Ethiopia

Support

The Royal Society, The Royal Society of Chemistry, Crystal Faraday Partnership, EPSRC, the Science Faculty of Addis Ababa University, the Ethiopian Science Technology Commission (ESTC), and The Ethiopian Cleaner Production Centre (ECPC) are acknowledged for financial support. The Green Chemistry Institute of the American Chemical Society is also acknowledged for the provision of workshop manuals and literature.

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Green challenges: student perspectives from the 2004 ACS-PRF Summer School on Green Chemistry

Selma Bektesevic,[a] Julie C. Beier,[b] Liang Chen,[c] Nicolas Eghbali,[d] Stephanie King,[e] Galit Levitin,[f] Geeta Mehta,[g] Richard J. Mullins,[h] Jessica L. Reiner,[i] Ross Weikel,[f] Songwen Xie[j] and Erica Gunn*[k]

DOI: 10.1039/b501692b

Participants in the American Chemical Society-Petroleum Research Fund (ACS-PRF) Summer School on Green Chemistry discuss the topics covered and lessons learned during the week-long summer school held July 31 through August 7, 2004, at Carnegie Mellon University. An outline of the program is accompanied by a discussion of the challenges and needs of the field of green chemistry as seen by the participants. These include further education of the public as well as members of the scientific community, thorough research and rigorous publication standards, and the formation of a cooperative and collaborative group of researchers.

Introduction

The American Chemical Society-Petroleum Research Fund (ACS-PRF) Summer School on Green Chemistry was held July 31 through August 7, 2004, at Carnegie Mellon University. More than 100 students and faculty representing 23 countries participated in a series of lectures, laboratories, poster sessions, a grant workshop, and a debate. The problems associated with the use and generation of toxic substances were analyzed from both a chemical and engineering perspective, and the importance of teaching people to intentionally address the principles of green chemistry was emphasized.

Unlike the intensive training and exhaustive teaching usually encountered in graduate courses, the summer school coordinators aimed to create an instructive and enjoyable week of study focused on green chemistry. As stated by the host, Terry Collins, the goal was to give those present a general idea of the issues and implications involved in environmentally responsible chemical research. Students were not expected to memorize the principles of green chemistry, but rather to begin to understand the obstacles to sustainability and the applications of green chemistry in addressing these issues.

With this in mind, the seminars and various activities did not attempt to teach the intimate details of a few specialized topics, but rather aimed at giving a general overview of the field. It was therefore a good opportunity for those who were not familiar with the field to build up their background while those more familiar with the topics covered exchanged their knowledge and points of view.

Though intellectually stimulating and highly informative, lectures provide a relatively passive interaction with material. To enhance direct interaction with the practical aspects of a subject, a formal debate was organized on an issue with numerous chemical, economic and social ramifications. Participants considered the proposition, "Drugs that make people's lives better take precedence over environmental protection." The debate approach allowed students to confront a real-world situation and realize firsthand the difficulty of solving an issue with a variety of implications. In this particular example, those implications were not only scientific and financial but also social and humanitarian.

The debate effectively engaged participants in the process of understanding complex issues. Perhaps more importantly, participants also became aware of significant technological and economic barriers to the application of green chemistry in industrial processes. It is important to recognize these barriers when attempting to develop and implement alternative reaction processes.

The summer school participants were also actively engaged in several green chemistry laboratories designed for

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integration into undergraduate courses. The experiments included liquid CO_2 extraction, enantioselective biotransformation, ionic liquid synthesis, solventless aldol reactions, and catalytic oxidation of chlorophenols. These labs incorporated traditional methods and procedures, making them ideal teaching tools, as well as good examples of green chemistry. When implemented, these experiments will introduce green chemistry concepts into the undergraduate teaching lab.

In addition to the lectures, labs, and debate, the students were also offered the opportunity to attend a grant workshop led by Dr Robert Rich of the ACS-Petroleum Research Fund. This useful workshop allowed participants to learn and practice some of the grant-writing skills necessary for success in their future careers.

Education of graduate students

The system that educates our chemists must change if we are to change the profession. As a start, programs such as this summer school introduce green chemistry principles to young scientists. Going forward, green chemistry must become an integral part of both the classroom and research. Echoing the participants of last year's summer school,[1] we assert that green chemistry should be integrated into the curriculum and research of all universities in all scientific areas, including chemistry and engineering. Researchers must use green principles every day, and stress that a sustainable civilization depends on all people.

A sustainable civilization is one in which "the daily activities of the people who comprise the civilization can be carried on into the indefinite future without undermining the ability of future generations to live with at least a comparably advantageous welfare."[2] Clearly, this requires a change in the entire civilization, not just chemists. Thus the education of chemists, manufacturers, and other scientists, although imperative, is only one piece of the puzzle. Chemists must also be taught to share their knowledge of green principles with the public.

There are many forms of public education, ranging from disseminating information on consumer products to commercials on proper disposal of medications and other substances. One of the most effective methods is K-12 outreach. Early education about the nature and hazards of chemicals as well as their benefits has a formative effect on the perspectives of the consumers and policy-makers of tomorrow, as well as inspiring young students to pursue chemistry as a profession.

Existing challenges

Misconceptions about the nature of chemical research are prevalent both within the field and in the general public. Despite the heavy influence of chemistry in our everyday lives, few people see chemistry as an environmentally benign subject. The benefits of chemical advancements are rarely remembered or understood by the layperson. Instead, the public tends to see chemistry as a dangerous and intimidating field. Misunderstandings arise within the chemical community as well. Green chemistry is often seen as an inconvenience without benefit to the practicing chemist, and many respected researchers dispute its utility and necessity. There is a tendency to marginalize the dangers of the methods currently used and to insist that those seeking to change are doing so without strong scientific backing.

Even if a chemist accepts the ideas of green chemistry and seeks to follow its guidelines, many challenges arise. Though a chemist may prefer to use environmentally benign conditions, the procedures currently available are often not sufficient to allow a green synthesis. A chemist working under a deadline to create a new molecule cannot be expected to spend valuable time researching a new green method rather than use a more traditional method where the necessary procedure has already been developed and fine-tuned. Industrial competition and market demands continue to promote the "results by any means" concept. Until the green toolbox is more complete, chemists are unlikely to seek a green chemistry alternative. In order to encourage the research necessary to develop these tools, the chemistry community must be brought to accept green chemistry as a legitimate and necessary scientific field of study. This is beginning to occur, but only slowly.

Higher awareness of environmental issues has resulted in an increase in funding agencies addressing quality of life issues and promoting change in current research methodology. As a result, worldwide research aimed at the development of cleaner processing has begun. The responsibility to continue these efforts falls on the shoulders of politicians, the academy, and industry to embrace the programs that promote sustainability. Unfortunately, chemistry that does not support sustainability is being sold as green in some cases, which can tarnish the image of those doing good and thorough research in the field.

In spite of these issues, a number of scientists are doing elegant research in this area. Various articles from all areas of the field were brought to our attention during the course of the summer school so that we could recognize these efforts. We also realized that it is of utmost importance that the research be thorough, reported with full experimental detail, supporting information, and a well thought out description of how the new method surpasses the contemporary method. Rigorously refereed publications will help to validate the science being done, and to ease the concerns of those that feel that green chemistry is a fringe science.

On the same note, the review process for articles in green chemistry should perhaps be more rigorous than any other area of chemistry. Periodically, "quack" articles find their way into the scientific literature. For well-established fields these articles are regarded as outliers, having fallen through the cracks of the review process, and are subsequently ignored by most readers. However, in a new field such as green chemistry, a few too many of these outliers can create a poor impression. To increase the legitimacy of the field it is necessary to create strict review guidelines and encourage green chemists to publish only the most important, thoroughly written research articles that offer improvements over current non-green technology. This may help to encourage future scientists to examine the field carefully and perhaps begin to include green chemistry techniques in their own research.

The ultimate solution to the problems described above rests on the education of future generations of scientists and non-scientists alike. According to Professor Terry Collins, "When chemists teach their students about the compositions, outcomes, mechanisms, controlling forces, and economic value of chemical processes, the attendant dangers to human health and to the ecosphere must be emphasized across all courses."[3] The students have to be challenged and motivated to find more sustainable processes that do not sacrifice profitability. To achieve these goals, the principles of green chemistry should become a part of the chemistry curriculum in every educational institution, as well as becoming an integral part of our daily lives.

Creation of a community

Green chemistry is not a new branch of chemistry as much as it is a new philosophy to guide scientific work based on environmentally and socially responsible practices. Such an endeavor will succeed best in a cohesive community. Progress will occur only if efforts are directed toward sustainability on all sides.

One of the aspirations of the summer school was the creation of such a community. The main goal was to bring students together from different disciplines and around the world to stand behind one objective: the improvement of our science to remove unnecessary hazards from our daily lives.

The summer school was open to graduate students and post-docs in chemistry and chemical engineering and attracted students from both fields in nearly equal proportions. During the entire week, students worked together and enriched the discussion with their experience. The presentations did not focus exclusively on either green engineering or green chemistry but rather on a mix of both areas. Participation of leading specialists from different backgrounds (academic as well as industrial) was a large asset. Presentation of green chemistry/green engineering from these varied viewpoints painted a complete and comprehensive picture of the field.

Synthetic design by a chemist and a chemical engineer will necessarily be different as each gives priority to different considerations. Knowledge of all the potential problems and challenges is a requisite for both the chemist and the chemical engineer who wish to succeed in the design of a clean and greener process. There has historically been a rift between the two groups, largely due to this difference in approach. The common problems related to lack of compromise were raised and discussed in order to demonstrate the need for cooperation to achieve sustainable processes.

The lecturers posed a challenge to both groups. They suggested that the measure of a good chemist is not in how many new compounds an individual has synthesized but rather how many steps are involved in the synthesis, the yield of the product, and the solvents used. Synthesis of one compound in yield close to maximum, going through the most efficient route and using benign solvents is better than the synthesis of many compounds that may pose problems to future generations due to waste and possible toxicity issues. Engineers were challenged to design processes that are more energy efficient. Careful attention to such details will lead to much greener processes, and may therefore have a large impact on the environment.

The objective of the summer school was to create a network among students having different areas of expertise, thus promoting cooperation in the field. Green chemistry presents us with many new challenges. Meeting the demands of these challenges will require competence in many fields, sometimes far from chemistry or chemical engineering. To ensure success, cooperative and interdisciplinary work will be a keystone in the strategies developed.

Of course, the community established is not composed entirely of students. The lecturers in the summer school were all renowned scientists; some were professors, some were from industry, and others represented professional societies. This allowed students to meet leaders from all parts of the field. In the future, students may be able to work with these excellent mentors in their attempts to create a better future. Also, having representatives from industry allowed us to see that some companies are actually applying the principles of green chemistry to their processes. Some of the students now aspire to work for these companies because of the good work practices they have.

The summer school successfully attracted both multidisciplinary and international participants. With the formation of such networks, it is reasonable to believe that one day the trends toward sustainable practices will be followed in the hope of reaching a truly sustainable society.

Conclusions

The Green Chemistry Summer School was very effective in making participants aware of the multitude of problems that exist, and the challenges that face those that wish to develop solutions. It also showed that the problems can be solved if we dedicate ourselves to the task. Though we may be forced to take small steps at first, success cannot fail to follow if we work together and share our experience and expertise.

Awareness of the issues at hand led to discussion among the students about the work we do. We all asked ourselves whether our work is actually sustainable, and whether there is a better way. An individual does not possess enough knowledge of all the aspects of the process, but we can ask someone with different expertise for help. This will involve different groups normally less exposed to the ideas of green chemistry and engineering, and will serve to spread the practices of green chemistry to the community.

The students who participated in the summer school will be the researchers and educators of tomorrow. Whether in academia or in industry, they are more likely than their peers to incorporate the principles of green chemistry into their work. They are assets to society because they will strive to create sustainable processes. Last, but not least, the students present were of different nationalities. Many of them will go back to their countries to work, and with them they will take the awareness and knowledge of green chemistry and engineering practices. This will ensure that the trend toward sustainable practices will become global and increase the probability of a truly sustainable society in the future.

Although the days were packed full of lectures, labs, and workshops, the participants were also allowed time for

non-academic interaction, such as soccer games and recreation time. The week ended with a beautiful riverboat cruise, which gave us the opportunity to reflect on the friendships that were made. We spent this time with our new colleagues who share similar goals: educating ourselves about the importance of green chemistry, and sharing the information gained with others. Improving the public perception of chemistry requires an interdisciplinary approach, and the summer school was an excellent opportunity to bring people with a variety of backgrounds from all over the world together to plan for a greener future.

The summer school brought a group of students together and helped them to define new goals for their future research. Together we gained the tools and skills needed to address the problems related to the design of sustainable processes. Although differences in method exist within any group composed of engineers and chemists, they are not insurmountable. The prize for this work is the world we leave to future generations.

Student participants

Takiya J. Ahmed, University of Oregon
Jessica L. Anderson, University of Notre Dame
Travis M. Anderson, Emory University
Fernando Dini Andreote, University of São Paulo
Salil Arora, Michigan State University
Gisela Mariana Arzac, Universidad de Buenos Aires
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Selma Bektesevic, University of Toledo
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Liang Chen, Tulane University
Delroy R.P. Coleman, Queens College of the City University of New York
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Stephanie King, Ohio University
Marc A. Klingshirn, University of Alabama
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Alexandre M. Latulippe, University Laval
Galit Levitin, Georgia Institute of Technology
Lorena Carvalho Martiniano, Federal University of Maranhao—UFMA
Dario M. Martino, Michigan State University
Geeta Mehta, Michigan State University
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Highlights

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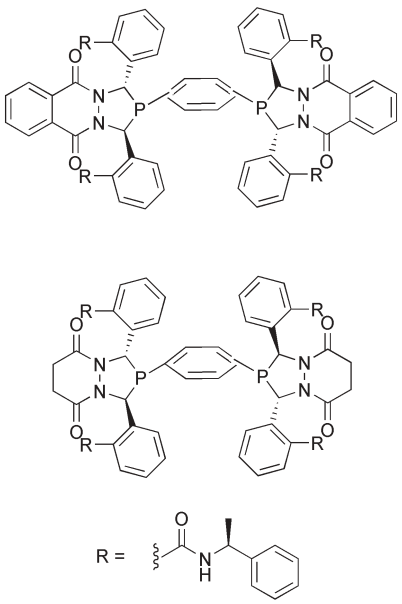
Markus Hölscher reviews some of the recent literature in green chemistry

Highly active and enantioselective hydroformylation with Rh catalysts

The hydroformylation is one of the atom efficient reactions showing a high potential with regard to sustainability. It is already operated in industry and the generated product—an aldehyde—is very well suited for further transformations. The challenge is the development of ligands/catalysts which are highly active and efficiently control regioselectivity favoring the production of the branched product in an enantioselective manner. Landis *et al.* from the University of Wisconsin synthesized novel bis-3,4-diazaphospholane ligands which upon complexation with rhodium form very active catalysts which enable hydroformylation of not only one substrate enantioselectively but three different olefins: styrene, allyl cyanide and vinyl acetate (*J. Am. Chem. Soc.*, 2005, **127**, 5040–5042).

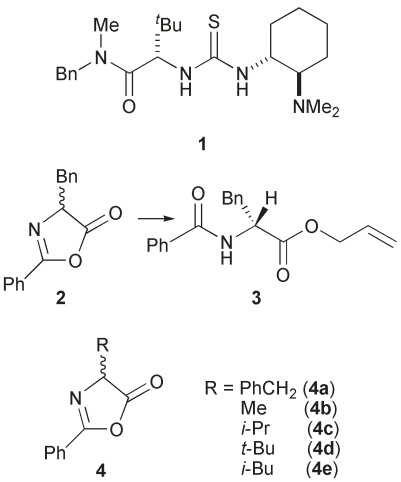


It is interesting to note that well known ligands such as ESPHOS or Kelliphite which have proven to operate with high enantioselectivities are in general only useful for one or two of the three substrates. BINAPHOS is the only exception with regard to enantioselectivity, but the turn over frequencies are around 200 h^{-1} for all substrates. In contrast the new diazaphospholanes are useful for highly enantioselective and regioselective hydroformylations of all three substrates with average turn over frequencies of *ca.* 3000 h^{-1}. Comparative experiments with different diastereomers of the ligands employed indicate that the stereochemistry of the phospholane ring controls the absolute chirality of the product rather than the stereochemistry of the chiral amine.

Enantioselective dynamic kinetic resolution of azlactones with second generation organocatalysts

Natural and non-natural α-amino acids are interesting starting materials for the synthesis of chiral ligands, pharmaceuticals and catalysts. Generally applicable methods for their production comprise asymmetric synthesis and dynamic kinetic resolution (DKR) of racemic precursors. Azlactones are an interesting group of compounds for the DKR yielding α-amino acids and very recently Berkessel *et al.* from the University of Cologne have added a promising group of organocatalysts enabling the DKR of *tert*-leucine-derived azlactones with allyl alcohol with high enantioselectivities. Proceeding with their work they have now introduced modified catalyst structures of which the most promising candidate is thiourea **1**, enabling the DKR of azlactone **2** to yield α-amino acid derivative **3** with 78% ee and a conversion of 59% at room temperature (*Chem. Commun.*, 2005, 1898–1900).

This is the highest enantioselectivity achieved in the DKR of **2** known to date. The catalyst is applicable quite generally, as the DKR of compounds **4** yields ee values between 78 (**4a**) and 95% (**4d**) with moderate to high conversions.



Transition metal nanoparticle fragmentation by laser irradiation in ionic liquids

One of the problems encountered frequently in catalytic applications of transition metal nanoparticles is the instability towards aggregation and formation of large particles, which usually changes the catalytic properties or even leads to inactive materials. Ionic liquids (ILs) have proven to be well suited solvents for the stabilization of metal nanoparticles, although even in IL-phases aggregation cannot be suppressed completely in many cases. Dupont *et al.* from the Institute of Chemistry and Physics, Brazil reasoned that laser irradiation of large nanoparticles dissolved in ILs could lead to fragmentation and generation of smaller particles (*J. Am. Chem. Soc.*, 2005, **127**, 4588–4589). Rhodium and palladium nanoparticles were prepared by reduction of suitable metal salts with hydrogen. The IL chosen was 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (BMI.PF_6). The solutions darken after 15 min (Pd) and 60 min (Rh) indicating the aggregation of the nanoparticles to large particles, which was shown by TEM analysis of the solutions (*ca.* 12 and 15 nm particle diameter, respectively).

However, irradiation of these solutions with a NdYAG laser at 532 nm and a fluence of 200 mJ cm^{-2} (8 ns pulses, 20 Hz) for 120 min afforded much smaller particles with approximate sizes of 4.2 (Pd) and 7.2 nm (Rh), which were stable in IL solution for prolonged periods of time (8 weeks for the Rh solutions). Laser irradiation of agglomerated large particles is thus a convenient tool for the fragmentation of these particles to small ones and in the future it might also allow the systematic variation of particle sizes and shapes, which would be very interesting for nanoparticle catalysis.

Syntheses of water-soluble *N*-donor ligands for aqueous catalysis using green, Michael-type addition reactions†

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A new route for synthesizing sulfonate-containing *N*-donor ligands has been developed involving the Michael-type addition reaction of primary or secondary amines with sodium vinylsulfonate in water. Our reactions offer several advantages over traditional Michael-type addition reactions. For example, while most conjugate addition reactions are carried out in organic solvents in the presence of bases or acids (S. G. Davies, T. D. McCarthy, *Synlett*, 1995, 700–704; D. Rosenthal, G. Braundrup, K. H. Davies, M.E. Wall, *J. Org. Chem.*, 1965, 30, 3689–3696),[1] our reactions adhere to green chemistry principles and are conducted in aqueous solutions without harsh bases or acids, eliminating the need for more toxic compounds and solvents. Additionally, the new synthetic route utilizes selective conjugate addition reactions instead of unselective alkylation reactions using sodium 2-bromoethanesulfonate or similar sulfonated alkyl halides (J. March, *Advanced Organic Chemistry: reactions, mechanisms and structure*, Wiley, New York, 4th edn., 1992, pp. 411-413),[2] which greatly decreases the amount of undesired side-products. Finally, the new synthetic route yields new, water-soluble ligands which may be utilized in aqueous catalysis involving water-soluble metal complexes.

Introduction

Water-soluble ligands, which can allow metal catalyzed reactions to take place in water, have been of significant interest in catalytic studies.[3] Most ligands that are specifically designed for water-solubility contain hydrophilic groups such as carboxylate or sulfonate moieties to increase the solubility of the organic molecules in water.[3] We are interested in preparing water-soluble *N*-donor ligands containing sulfonate groups for synthesizing metal complexes that can catalyze the hydrolysis of organic molecules such as esters, phosphate esters, and amides in water. Catalytic hydrolysis of organic molecules has been of great interest for many reasons. One motivation for studying the catalytic hydrolysis of esters, amides, and phosphoester compounds by synthetic metalloenzyme mimics comes from the desire to better understand metallohydrolases through bio-inorganic model studies.[4] The hydrolysis of organophosphate compounds is also of interest as a possible means for destroying unwanted stockpiles of organophosphate-based chemical warfare nerve agents.[5] Another driving force for studying the hydrolysis of organophosphate compounds by metal complexes lies in the fact that these studies may lead to better methods for the cleanup of water supplies which are contaminated by phosphotriester-based insecticides.[6] In addition to better understanding the nature of nucleases that catalyze the hydrolysis of DNA or RNA and for designing artificial nucleases,[7] another medically relevant metallohydrolase is β-lactamase, which catalyzes the hydrolysis of β-lactams and is responsible for bacterial resistance to β-lactam antibiotics.[8]

The conjugate addition of nucleophiles to electron-deficient olefins is well-known in organic synthesis.[9] While the addition reactions of amines[10] and amides[11] to vinylic compounds conjugated to neutral electron-withdrawing groups are known, there have been no reports of such conjugate addition reactions of amines towards vinylic compounds containing an anionic group such as the sulfonate moiety. The negative charge on the sulfonate group might be expected to block the conjugate addition reaction; here we report that this is not the case. We report the successful synthesis of water-soluble *N*-donor ligands **1–4** *via* Michael-type additions of various amines to sodium vinylsulfonate in water and the X-ray crystal structure of a Zn(II) complex, **5**, ligated by one of the new, water-soluble *N*-donor ligands and preliminary catalytic data on the hydrolysis of 4-nitrophenyl acetate by **5**.

Results and discussion

We first attempted to synthesize **1** (Table 1) by alkylating the secondary amine *N*-atom of 3,3′-iminobis(*N*,*N*-dimethylpropylamine) with sodium 2-bromoethanesulfonate. These reactions led to complex mixtures of products, most likely due to unselective alkylation of both the tertiary and secondary amine *N*-atoms, forming quaternary ammonium compounds as well as the desired tertiary amine **1**.[2] Wieghardt and co-workers also reported difficulties isolating the desired product when preparing 1,4,7-triazacyclononane-*N*,*N*′,*N*″-tris-2-ethanesulfonate by alkylating 1,4,7-triazacyclononane with sodium 2-bromoethanesulfonate, presumably due to overalkylation and the formation of quaternary ammonium compounds.[12] Therefore, instead of utilizing 2-bromoethanesulfonate to achieve our synthetic goals, we developed new Michael-type reactions for the conjugate addition of amines to sodium vinylsulfonate in aqueous solutions which are selective for primary and secondary amines and do not lead to quaternary ammonium products.

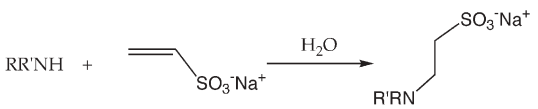
The reaction of 3,3′-iminobis(*N*,*N*-dimethylpropylamine) in a refluxing 25 wt% solution of vinylsulfonic acid sodium salt in

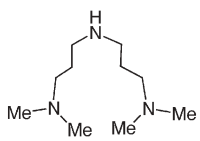
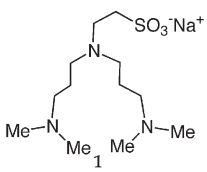
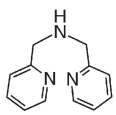
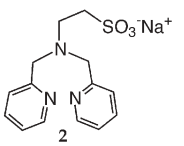
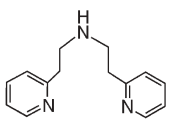
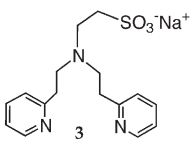
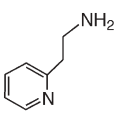
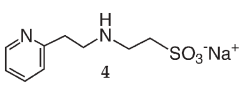
† Electronic supplementary information (ESI) available: Experimental details and results of kinetic studies of the hydrolysis of 4-nitrophenyl acetate by complex 5. See http://www.rsc.org/suppdata/gc/b5/b500264h/

water led to the formation of ligand **1** in 78% yield after 5 days (Table 1). Similar yields and reaction times were also obtained when other secondary amines such as di-(2-picolyl)amine and bis[2-(2-pyridyl)ethyl]amine reacted with sodium vinylsulfonate to form ligands **2** and **3**, respectively. Not surprisingly, the reaction of the primary amine 2-(2-aminoethylpyridine) with sodium vinylsulfonate proceeded much more quickly than the reactions involving secondary amines, and the synthesis of the secondary amine **4** was completed within one day. No tertiary amine side-product was isolated in the synthesis of **4**, probably due to the relatively slow kinetics of the formation of tertiary amines compared to secondary amines in these types of conjugate addition reactions.

The syntheses of **1–4** require longer reaction times and higher temperatures than standard Michael-type addition reactions of amines towards vinylic compounds with neutral electron withdrawing groups, which typically only require a few hours for completion. The lower reactivity of sodium vinylsulfonate compared to neutral vinylic compounds may in part be attributed to the anionic nature of the sulfonate moiety. Despite the longer reaction times and higher temperatures, our reactions offer several advantages over traditional Michael-type addition reactions. For example, while many conjugate addition reactions are carried out in organic solvents in the presence of bases or acids,[1] our reactions adhere to "green synthesis" principles[13] and are conducted in aqueous solutions without harsh bases or acids, eliminating the need for more toxic compounds and solvents.

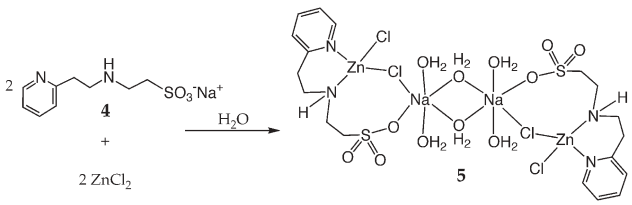
Table 1 Green syntheses of new, water-soluble *N*-donor ligands *via* Michael-type addition of amines to vinylsulfonate



Entry	Starting amine	Product	Reaction time/d	Yield (%)
1			5	78
2			3	74
3			4	58
4			1	86

In addition to the advantages of the new, "green" synthetic routes to form **1–4** and the syntheses of new complexes such as **5**, preliminary results also indicate that some of the metal complexes of **1–4** catalyze the hydrolysis of activated esters and phosphate esters such as 4-nitrophenyl acetate and bis(4-nitrophenyl) phosphate in aqueous solutions, which may also be of environmental significance. For example, complex **5** is active in catalyzing

Ligands **1–4** bind readily to Zn(II), Cu(II), and Ni(II) to yield water-soluble metal complexes. One of these metal complexes, synthesized by the binding of **4** to $ZnCl_2$ to form the water-soluble complex **5** (Scheme 1), has been characterized by single crystal X-ray crystallography (Fig. 1).‡ The X-ray crystal structure of **5** (Fig. 1) shows that it is a dimer in the solid state, with distorted tetrahedral geometry around each Zn(II) center, which is ligated by a pyridyl nitrogen atom N1, an amine nitrogen atom N2, and two chloride ligands Cl1 and Cl2. One of the sulfonate *O*-atoms and a chloride ligand are bound to a Na^+ ion, which is coordinated by two terminal (O4 and O6) and two bridging (O5 and O5A) water molecules forming a centrosymmetrical dimeric unit (Fig. 1).



Scheme 1

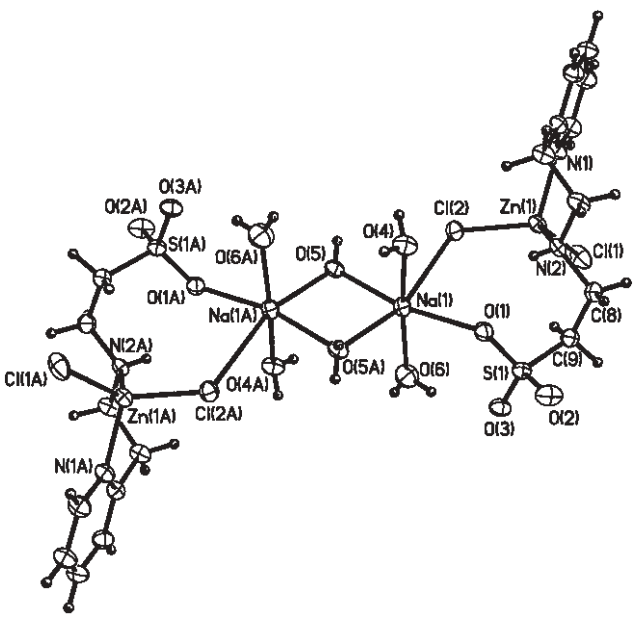


Fig. 1 An ORTEP diagram of **5**. Selected bond distances (Å) and angles (degrees): Zn1–N1, 2.0411 (17), Zn1–N2, 2.0538 (17), Zn1–Cl1, 2.2200 (6), Zn1–Cl2, 2.2326 (5), Na1–Cl2 3.009 (1), Na1–O1 2.388 (2), Na1–O4 2.399 (2), Na1–O5 2.371 (2), Na1–O5a ($-x$, $1-y$, $-z$) 2.362 (20); N1–Zn1–N2 100.12 (7), N1–Zn1–Cl1 107.13 (5), N2–Zn1–Cl1 114.02 (5), N1–Zn1–Cl2 109.63 (5), N2–Zn1–Cl2 104.42 (5), Cl1–Zn1–Cl2, 119.77 (2), Cl2–Na1–O1 89.75 (5), O5–Na1–O5a ($-x$, $1-y$, $-z$) 85.63 (6).

the hydrolysis of 4-nitrophenyl acetate, NA. At 25 °C, pH 7.4, $I = 0.10$ ($NaNO_3$) in 10% v/v CH_3CN, **5** has an observed second-order rate constant of 2.03×10^{-2} M^{-1} s^{-1} (see electronic supplementary information†). While the activity of **5** in catalyzing the hydrolysis of NA is modest, it is comparable to that of many other Zn(II) complexes reported in the literature.[14] It is postulated that as we synthesize other metal complexes of **1–4** with anions that are more weakly coordinating than Cl^-, we may be able to obtain more active catalysts.

Conclusion

In summary, new sulfonate-containing water-soluble ligands **1–4** have been synthesized *via* previously unknown Michael-type addition reactions of both primary and secondary amines with sodium vinylsulfonate. These syntheses are conducted using environmentally benign methods in water and do not require harsh bases or acids. We have also structurally characterized a new Zn(II) complex **5** using one of these new ligands. Initial experiments show that **5** catalyzes the hydrolysis of organic substrates such as 4-nitrophenyl acetate in aqueous solutions. We are currently conducting detailed investigations of catalytic reactions with other complexes and substrates and are exploring the differences in catalytic abilities of the metal complexes as a function of the varying ligands as well as examining the effects of the anions on their catalytic abilities. It is anticipated that these new types of ligands will lead to further developments in aqueous catalysis chemistry.

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‡ Compound **5**. C_9 H_{19} Cl_2 N_2 Na O_6 S Zn, M = 442.58, monoclinic, $a = 18.3353(10)$, $b = 7.6965(4)$, $c = 12.7734(7)$ Å, $U = 1747.88(16)$ $Å^3$, $T = 150(2)$ K, space group $P2_1/c$ (no. 14), $Z = 4$, μ(Mo–K_a) = 1.880 mm^{-1}, 10766 reflections measured, 4038 unique ($R_{int} = 0.0220$) which were used in all calculations. The final $R1$ and $wR2$ were 0.0302 and 0.0723($I>2\sigma I$).CCDC reference number 268563. See http://www.rsc.org/suppdata/gc/b5/b500264h/ for crystallographic data in CIF or other electronic format.

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Ultra-deep desulfurization of transportation fuels *via* charge-transfer complexes under ambient conditions

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Very stringent regulations on the maximum sulfur content of gas oil have led to intense research into all aspects of desulfurization. Deep desulfurization of diesel fuels is particularly challenging due to the difficulty of removing refractory sulfur compounds, particularly 4,6-dialkyldibenzothiophenes, using conventional hydrodesulfurization processes (HDS). A novel approach to the potential desulfurization of fuels such as diesel is proposed. It relies on the ability of 4,6-dialkyldibenzothiophene to form charge-transfer complexes (CTC) with π-acceptor molecules. We present the synthesis of a new π-acceptor molecule, 4,5-dicyano-2,7-dinitrofluorenone, solution redox behaviour and the crystal structure of the charge-transfer complex with the refractory 4,6-dimethyldibenzothiophene. This π-acceptor compound was then immobilized on a hydrophobic support (poly(styrene-co-divinylbenzene)). The selectivity of the CTC process was confirmed by the analysis of the sulfur compounds trapped from straight run Arabian Light (SR) containing 13600 ppm S. The functionalized polymer can be used in multiple cycles for the removal of refractory S-containing compounds from hydrotreated SR. It can also be regenerated with toluene. The high selectivity of this material permits diesel fuel to be desulfurized to a level that meets future regulatory requirements, *i.e.* less than 10 ppm S, at ambient temperature and without hydrogen consumption.

Introduction

In recent years, deep desulfurization of diesel fuel has attracted much attention due to the gradual reduction of the statutory sulfur content in most western countries. In 2009, the maximum S-content within the European Union will be reduced to 10 ppm compared to today's value of 350 ppm.[1,2] Heightened interest in ultra-clean fuels is also driven by the need for new emissions control technologies for IC engines (especially those for diesel fuels), and the use of on-board or on-site reforming of hydrocarbon fuels for new fuel cell vehicles.[3]

There are three major types of transportation fuels: gasoline, jet fuels and diesel, which differ in composition and properties. The common types of sulfur compounds in the diesel fuel range are alkylated benzothiophenes (BTs), dibenzothiophene, and its alkylated derivatives (DBTs) (Fig. 1).

The state of the art in desulfurization technology is hydrodesulfurization (HDS). In this process, the sulfur is removed from sulfur containing compounds by reaction with hydrogen, forming H_2S on a sulfur type active phase catalyst. HDS is effective for a range of sulfur containing compounds that exhibit varying reactivities towards desulfurization. Reactivity is dependent upon the local environment of the sulfur atom in the molecule, and the overall shape of the molecule. The process is widely employed throughout the world and has been used for over 60 years. HDS is highly efficient at removing thiols, sulfides and disulfides, but is less effective for aromatic thiophenes and thiophene derivatives, especially those containing functional groups that hinder the sulfur atoms. Due to the current 350–500 ppm specifications mandated in several countries, the diesel fuel range available today has low total sulfur content but a disproportionately high concentration of refractory sulfur species.

Improvement of today's technology to enable production of ultralow sulfur content fuel requires that the difficulty of desulfurizing refractory sulfur compounds be overcome. Investigations have demonstrated that the sulfur compounds remaining in diesel fuels with a sulfur level lower than 500 ppm are the dibenzothiophenes with alkyl substituents at the 4- and/or 6-position, (Fig. 1). Both steric hindrance and electronic factors are responsible for the observed low reactivity. To meet the new regulations, the refining industry has demonstrated its capability to adapt hydrotreatment to the stringent regulations by improving catalytic activity and increasing the process severity, especially by increasing the hydrogen pressure or designing new reactor configurations.[4] However, the selective elimination of this family of compounds from fuel is difficult due to their relatively low concentration in the feed and their low reactivity towards catalytic hydrodesulfurization.

The elimination of refractory sulfur compounds by non-catalytic processes is becoming a new challenge, because it could be accomplished at ambient temperature and pressure and without leading to an increase in the hydrogen consumption. New process concepts[3] include design approaches for ultra-deep desulfurization focusing on adsorption,[5–7] selective extraction using ionic liquids,[8–10] oxidation-extraction,[11,12] precipitation of S-alkylsulfonium salts[13] and biodesulfurization.[14]

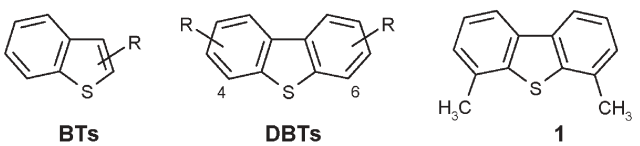

Fig. 1 Types of sulfur compounds present in the diesel fuel range.

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The planarity and electron-rich structure of 4,6-dimethyldibenzothiophene **1** (Fig. 1), lead us to expect that it would be capable of forming charge-transfer complexes (CTCs) with suitable π-acceptors. Charge-transfer complexes (CTCs) arising from the interaction of aromatic π-donor and π-acceptor molecules have been studied extensively[15] and recently charge-transfer complex interactions have been evidenced by chemical force microscopy.[16] CTCs have been used in supramolecular chemistry,[17] for chiral recognition,[18] and for selective organic transformation.[19]

An adsorption process is being explored in our laboratory for ultra-deep desulfurization of distillate fuels based on selective removal of electron rich refractory sulfur compounds like 4,6-dimethyl dibenzothiophene **1** (Fig. 1) by charge-transfer complex formation.[20] However, diesel fuel contains a large variety of aromatic compounds, with and without heteroatoms, that compete with **1** in the formation of CTCs. Theoretical calculations[21] and experimental studies on synthetic and real feed[22–25] have shown that symmetrical π-acceptors based on polynitrosubstituted 9-fluorenones (*e.g.* 2,4,5,7-tetranitro-9-fluorenone **2**, Fig. 2) efficiently and selectively complex dibenzothiophenes in preference to benzothiophenes and aromatic compounds.

Polynitrosubstituted 9-fluorenones (Fig. 2) have been widely employed as acceptors for charge-transfer complex formation,[16] as photosensitizers and in electron transport materials.[26] The structure of acceptor **2** has been determined by single X-ray analysis and reveals significant steric strain between the nitro substituents in the 4- and 5- positions.[27] Thus their acoplanarity with the fluorene nucleus probably leads to a decrease in the electron-acceptor efficiency of these groups on account of the reduction in their contribution to the conjugation effect,[27] and could interfere with the formation of a CTC.[21]

With the objective of improving the selectivity and the efficiency of the complexation of 4,6-dialkyldibenzothiophene, we carried out the synthesis of planar symmetrical π-acceptors bearing less bulky electron-withdrawing groups in the 4- and 5- position. It was expected that the substitution of nitro groups in the 4- and 5-positions by linear cyano (compound **4**, Fig. 2) groups would decrease the steric strain and thus the dihedral angle between the two aromatic rings. Then, we determined their redox properties and studied the crystal structures of the new fluorenone derivatives and the CTC complex formed by π-acceptor **4** and refractory compound **1**. Compound **4** was then immobilized on an insoluble resin for the ultra-deep desulfurization of distillate fuels by solid–liquid extraction.

Results and discussion

Synthesis of the π-acceptor molecule 4

Acceptor **2** is known to react with various proton-containing nucleophiles with substitution of the nitro group.[26–28] However, substitution occurs mainly in the 2- and 4- positions[28] and introduction of the cyano group involves the use of HCN. We prefer to study a two step procedure starting from 2,7-dinitro-9-fluorenone **6** (Fig. 3), readily accessible from fluorenone. Methods for bromination of strongly deactivated aromatics derivatives are scarce.[29–31] Compound **7** had previously been prepared using a mixture of mercury(II) nitrate and bromine.[29] We found that **6** could be brominated in a concentrated H_2SO_4–CF_3CO_2H mixture with NBS[31] to yield 4,5-dibromo-2,7-dinitrofluorenone **7** which was then converted into 4,5-dicyano-2,7-dinitrofluorenone **4** by reaction with CuCN in DMF solution.

Electrochemistry

The redox properties of the π-acceptor **4** were compared to π-acceptor **2**, **3** and **5**[32] (Fig. 2). We conducted cyclic voltammetry (CV) measurements in acetonitrile at room temperature with $Bu_4N^+BF_4^-$ as the supporting electrolyte (Fig. 4). The redox potentials of compounds **2**, **3**, **4** and **5** are summarized in Table 1.

By analogy with compounds **2**, **3** and **5**, π-acceptor **4** shows clear amphoteric multiredox behaviour (Fig. 4, Table 1), consisting of 3 reversible single electron reduction waves.

Replacement of the nitro groups by cyano groups at the 4- and 5- positions slightly decreases the electron acceptor properties: the first reduction of compound **4** is shifted to a more positive value by 0.15 V (Table 1), but electron affinity (EA) calculations indicate that **4** is a rather strong acceptor, comparable to the strongest known acceptor of the fluorene series, *i.e.* 2,4,5,7-tetranitro-9-dicyanomethylene-fluorene[32] or **3**. The comparison of the reduction potentials for compounds **5**[32] and **4** (Fig. 2) shows that the location of the cyano substituents (2,7 *versus* 4,5) does not exert a notable effect upon the electrochemical behavior of these compounds although a more planar structure, which is more favorable for CTC formation, was expected for compound **4**.

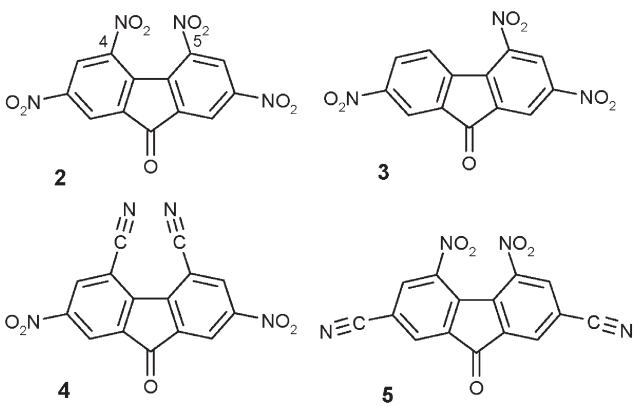
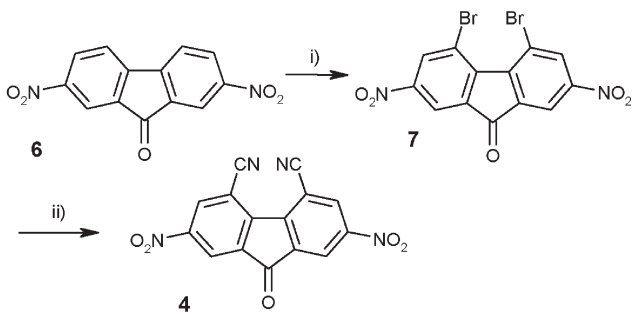


Fig. 2 Structure of π-acceptor molecules.



(i) NBS, CF_3CO_2H / H_2SO_4, 65°C, 24 h, 82%; (ii) 3.3 eq. CuCN, DMF, 80°C, 4H, 56%

Fig. 3 Synthesis of the acceptor **4**.

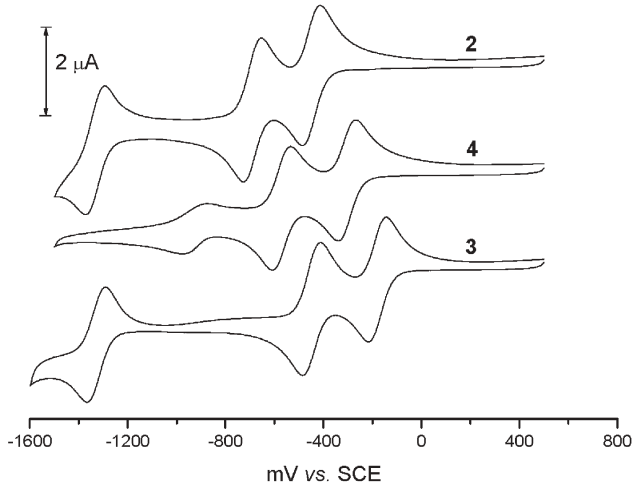


Fig. 4 Cyclic voltammogram of compounds **2**, **3** and **4** under the conditions stated in Table 1.

Table 1 Cyclic voltammetry data for π-acceptors **2**, **3**, **4**[32] and **5**

Compd	$E_{1red}^{1/2}$/V	$E_{1red}^{1/2}$/V	$E_{1red}^{1/2}$/V	EA (eV)[a]
2	−0.47	−0.71	−2.69	3.01
3	−0.20	−0.47	−1.35	2.74
5[32]	−0.27	−0.64	−1.33	2.27
4	−0.32	−0.59	−0.94	2.86

Solvent acetonitrile; electrolyte 0.2 M $Bu_4N^+BF_4^-$; scan rate 100 mV s^{-1}. All potentials given in the table were recalculated to Ag/AgCl scale.[a] Calculated using equation in ref. 32.

Single crystal X-ray analysis

It was noted that the substituents in positions 4 and 5 had a strong influence on the crystal structure of compounds **2**, **4** and **7**, and in particular, on the torsion angles listed in Table 2.

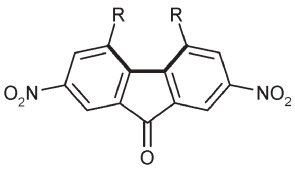
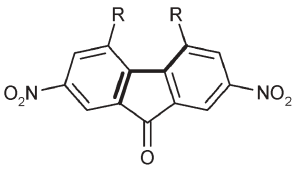
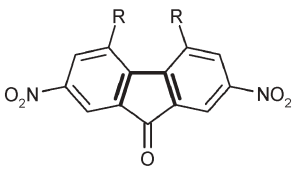
The X-ray structure analysis of compound **2** has already been determined.[33,34] The asymmetric unit consists of two molecules which differ slightly in their planarities and torsional angles. The two nitro groups in the 4- and 5- positions cannot remain in the fluorenyl plane and tend to move apart from one another. This repulsion causes rotation of these groups, inclination of C–N bonds and deformation of the fluorenone moiety. There are significant deviations from planarity of the fluorenone moiety of **2** in contrast to the planar molecule of 2,9-dinitrofluorenone **6**.[35] The dihedral angle values between the outer rings [C(4)–C(4a)–C(4b)–C(5)] (Fig. 5) of **2** are 13.5° and 7.7°[33] (Table 2) although it is equal to 1.5° for **6**.[35] This deviation from planarity of the fluorenone moiety of **2** is expected to minimize the CT interactions between planar electron rich compounds **1**[36] and **2**.[21] The same trend is amplified in compound **7**, bearing bulky bromides in the 4- and 5-positions (Table 2), which has a dihedral angle value of 25.6°. In compound **4**, introduction of the linear cyano groups in the 4- and 5- positions, strongly reduced the steric strain and the fluorenone moiety is almost planar. The dihedral angle between the outer rings [C(4)–C(4a)–C(4b)–C(5)] of compound **4** is 5.8° (Table 2).

CT complexation in the solid state

Solution studies of the charge-transfer complexes formed between compound **1** and fluorenone derivatives are severely limited by their very low solubility.[25] Single crystals of the charge-transfer complex were grown from a chloroform solution of equimolar amounts of compound **4** and **1**. Fig. 6 shows the packing diagrams.

The donor **1** and π-acceptor molecule **4** lie parallel with interplanar separation of 3.4 Å, which corresponds to the value expected of a charge-transfer interaction.[21] Surprisingly the interactions between **1** with π-acceptor **4** involve a distortion of the structure of **4**. An increase in the dihedral angles values between the outer rings [C(4)–C(4a)–C(4b)–C(5)] from 5.8° to 14.1° was observed for **4** (Table 2) although almost no modification was noticed for compound **1**. Fig. 7 shows the crystal packing of the CTC formed between compound **1** and π-acceptor **4**. The CTC crystal is composed of alternate layers of donors and acceptors. These layers are not coplanar for the same entity.

Table 2 Selected torsion angles from X-ray structure analysis acceptors **2** (two independent molecules),[33] **7**, **4** and the charge-transfer complex between **4** and **1**

Torsion angles studies[a]	Torsion angles values/° [2][33]	[7]	[4]	[4/1]
 C(4)-C(4a)-C(4b)-C(5)	13.5 7.7	25.6	5.8	14.1
 C(9a)-C(4a)-C(4b)-C(5) or C(4)-C(4a)-C(4b)-C(8)	166.5 167.8 174.1 173.1	162.3 160.1	174.3 176.9	169.4 169.5
 C(9a)-C(4a)-C(4b)-C(8a)	8.5 5.1	11.9	2.9	7.0

[a] For atom numbering, see Fig. 5

Immobilization of π-acceptor molecule on organic support

In order to check the feasibility of our concept for a deep desulfurization process, π-acceptor **4** was immobilized on a solid support according to Fig. 8. Formation of a hydrazone linker allows immobilisation on a solid support without substituting an electron-withdrawing group (nitro or cyano) at the fluorene moiety with an electron-donating group (alkoxy or alkyl). Furthermore,

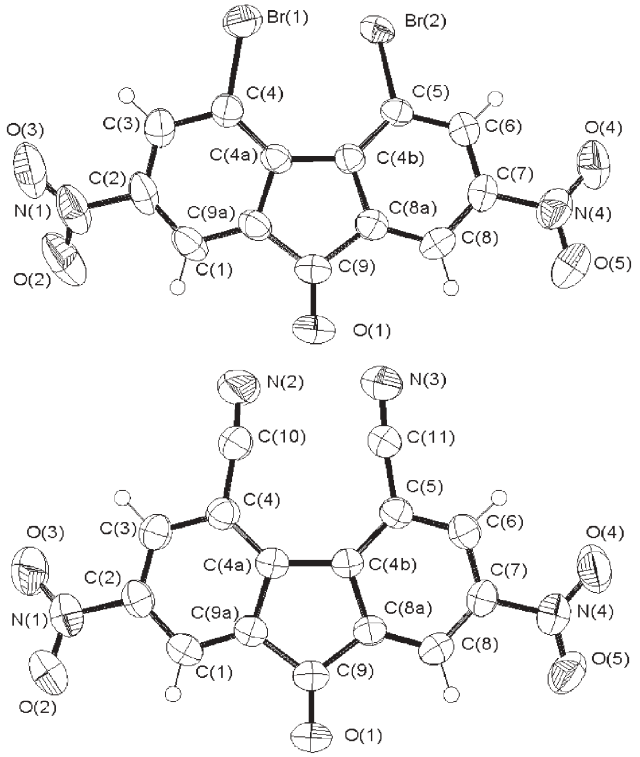


Fig. 5 Structure of the π-acceptor **7** (top) and **4** (bottom).

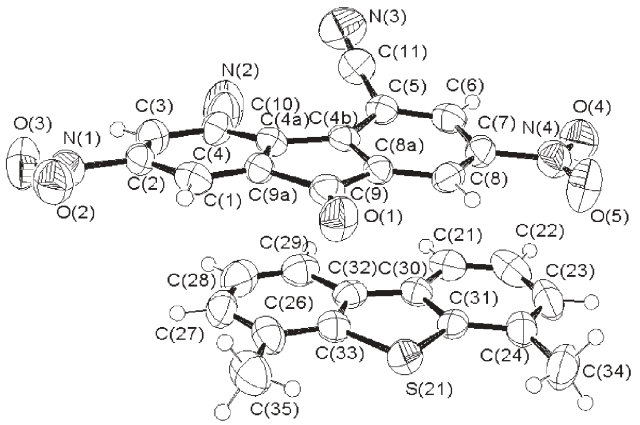


Fig. 6 Structure of the charge-transfer complex between 4,6-dimethyldibenzothiophene **1** and π-acceptor **4**.

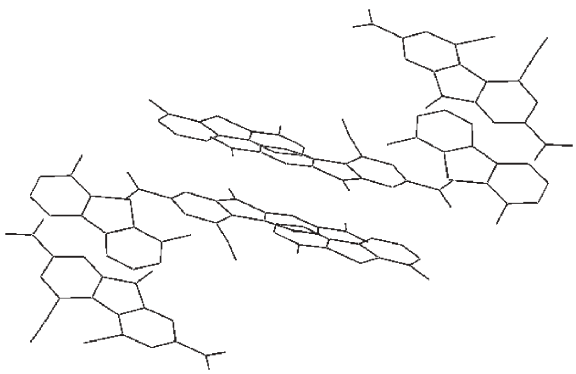
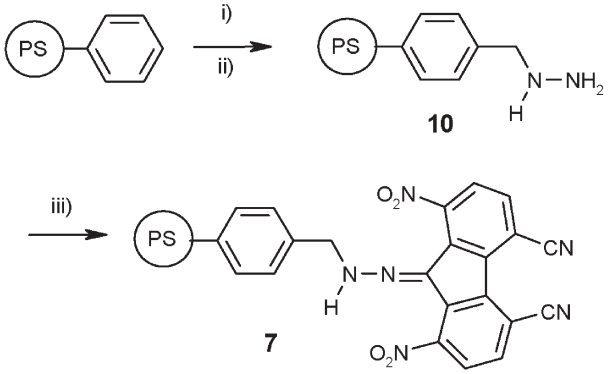


Fig. 7 Crystal packing of the CTC between compound **1** and π-acceptor **4**. H atoms are omitted.



i) CH_3OCH_2Cl, $TiCl_4$, $CHCl_3$, 24 h; (ii) H_2N-NH_2, EtOH, 60°C, 24 h; iii) **4**, toluene/AcOH (10/1), 75°C, 3 days

Fig. 8 Immobilization of π-acceptor **4** on poly(styrene) resin **7**.

this didn't modify the symmetry of the π-acceptor and is expected to be stable under the experimental conditions.

Poly(styrene) resins were chloromethylated (1.37 mmol Cl g^{-1}) and then treated with an excess of hydrazine (35% wt) in EtOH at room temperature to give methyl hydrazine polymer-bound resin **10**. π-Acceptor **4** was then added to resin **10** as a suspension in a toluene–acetic acid mixture at 75 °C. The excess of reagent was removed by soxhlet to yield resin **7**. The loading of resin **7** was determined by elemental analysis to be 0.4 mmol of π-acceptor **4** per g.

Desulfurization of diesel fuel range with immobilized π-acceptor molecules

To examine the selectivity of resin **7** towards dibenzothiophene derivatives, we studied the complexation procedure with straight run oil (SR) (Table 3) with the following sulfur content: 13600 ppm, 8600 ppm (63%) including benzothiophene derivatives (BTs) and 5000 ppm (37%) including dibenzothiophene derivatives (DBTs) (Fig. 9). The SR was treated with resin **7** in a batch reactor with continuous stirring. The sulfur content of the residual feed was determined and was found to be 10600 ppm S, which corresponded to an elimination of about 23% of the total sulfur. Resin **7** was regenerated by washing with toluene. The selectivity of the process toward DBTs could be confirmed by analysis of the toluene fractions (Fig. 9). A benzothiophene/4,6-dimethyldibenzothiophene selectivity higher than 40 could be calculated from the sulfur chromatogram. About 70 wt% of the compounds trapped by resin **7** are dibenzothiophene derivatives and 30 wt% are polyaromatics without heteroatoms. This result

Table 3 Composition and physical properties of straight run (SR) oil studied

	SR 13600	SR 390	SR 60
Density (288 K)/g l^{-1}	853	838	835
Sulfur (ppm)	13600	390	60
Total nitrogen (ppm)	104	29	6
Aromatics (wt%)	32.1	26.2	23.4

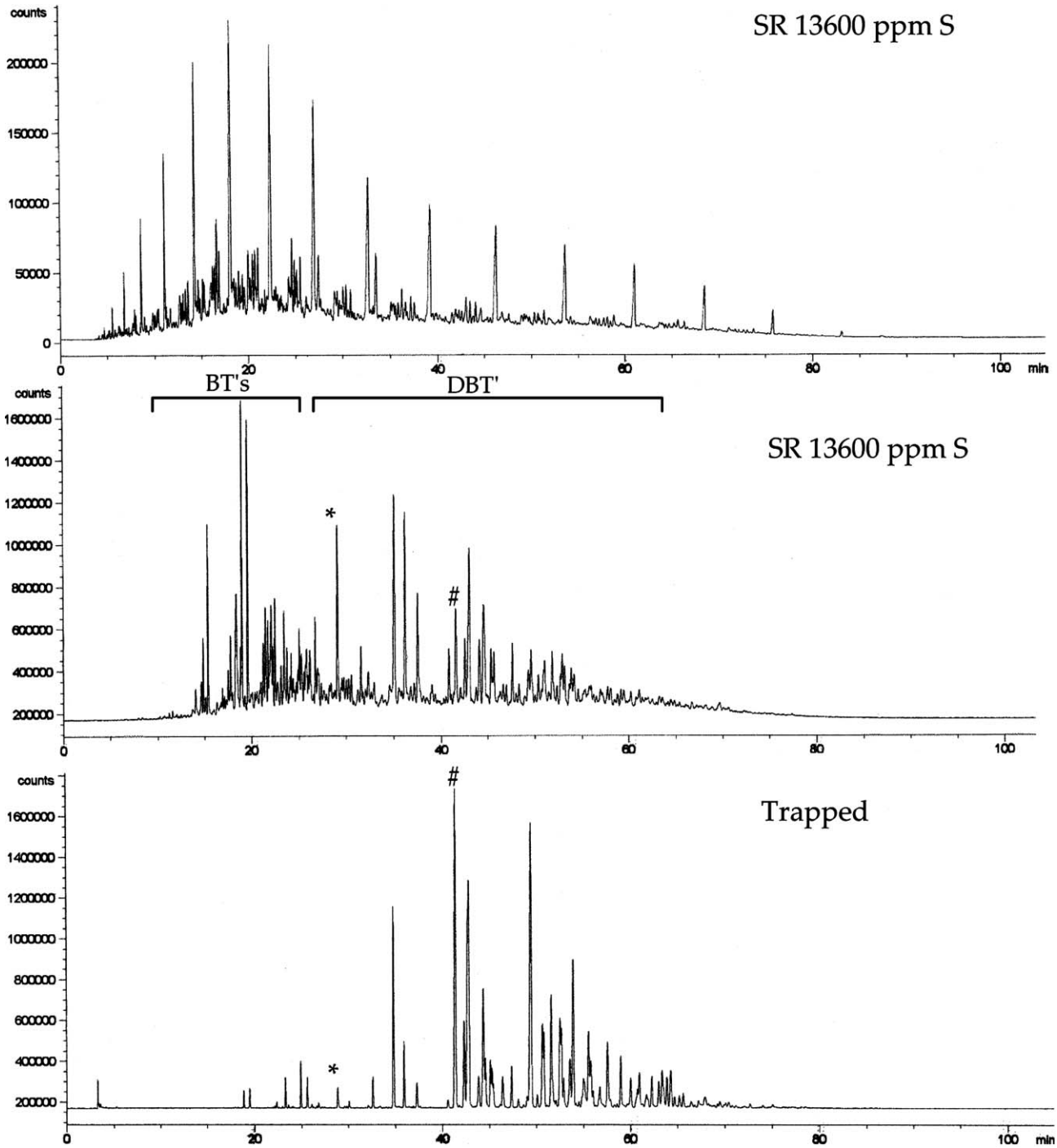


Fig. 9 Carbon and sulfur chromatograms of SR oil and sulfur chromatogram of trapped compounds. * and # correspond to benzothiophene and 4,6-dimethyldibenzothiophene respectively. *General conditions*: ambient temp., contact time 24 h, ratio fuel/polymer = 2.

highlights the selectivity of the CTC process towards refractory DBTs.

In order to reach very low sulfur levels we used a multistage extraction process with hydrotreated SR. The desulfurized oil from the first extraction step was re-treated with regenerated resin **7**. Resin **7** could be regenerated by back extraction with 5 resin volumes of toluene and could be reused up to 10 times without loss of activity.

This process was repeated up to four times with two hydrotreated SRs obtained after classical HDS and deep HDS (390 and 60 ppm S respectively). The results are summarized in Table 4.

As shown in Table 4, the results of experiments with hydrotreated SR are promising. In three steps, a fuel containing less than 50 ppm S was obtained starting from diesel with 390 ppm S. Resin **7** is effective even with low S content SR

Table 4 Multistage desulfurization of diesel oil[a]

Stage	Sulfur content (ppm)	
Initial	390[b]	60[c]
1	175	
		40
2	80	
		27
3	40	
		17
4		9

[a] *General conditions*: ambient temp., contact time 4 h. [b] Straight-run oil after classical HDS, ratio fuel/polymer = 2. [c] Straight-run oil after deep HDS, ratio fuel/polymer = 10.

(60 ppm S) obtained after severe HDS. The sulfur compounds remaining in the feed are refractory DBTs and in four steps the future specification was obtained (<10 ppm S).

Conclusions

The results presented show a new approach to the ultra-deep desulfurization of liquid fuel, with high selectivity towards the refractory substituted dibenzothiophenes that are very difficult to remove by common hydrodesulfurization techniques. The new method is based on the selective adsorption of dibenzothiophenes by formation of charge-transfer complexes with immobilized π-acceptor molecules. The application of very mild process conditions (low pressure, ambient temperature, no hydrogen consumption) is an additional advantage of this new approach in comparison to traditional HDS.

Experimental

Quantitative analysis of the total sulfur concentration was determined by energy X-ray fluorescence spectroscopy using a Horiba SLFA 1800 sulfur in oil analyzer, using 20 mm i.d. PTFE cells with 7 μm Mylar film windows. To eliminate the effect of the matrix on the gas oil, the apparatus was calibrated using a series of different gas oils containing between 100 and 13600 ppm of sulfur. Low sulfur and nitrogen concentrations were analyzed by UV fluorescence and by chemiluminescence, respectively, on an Antek 9000 Series nitrogen/sulfur analyzer equipped with a robotic liquid autosampler.

Qualitative analysis of the sulfur-containing molecules was performed using a gas chromatograph associated with a sulfur specific detector (Sievers Model 355 B SCD). For qualification of the components, the BT and the DBT were commercially available and various alkyldibenzothiophenes have been synthesized as previously reported.[37]

The relevant properties of straight run oil are summarized in Table 3.

2,4,5,7-Tetranitro-9-fluorenone (2)

A solution containing 20 g (72 mmol) of 2,7-dinitrofluorenone (**6**) and 200 ml of concentrated sulfuric acid was added dropwise to a mixture of 120 ml concentrated nitric acid and 120 ml concentrated sulfuric acid at 60 °C. The temperature was gradually increased from 60 °C to 130 °C. The mixture was stirred for 5 hours at 130 °C, cooled, then poured into cold water. The yellow solid was washed with water and dried. The solid was purified by recrystallisation from acetic acid yielding yellow needles (79%). Rf: 0.53 (CH_2Cl_2). ^{1}H NMR (200 MHz, δ DMSO d_6): 8.97 (d, J = 2.26 Hz); 8.77 (d, J = 2.26 Hz), ^{13}C NMR (50 MHz, δ DMSO d_6): 187.61; 150.56; 146.31; 140.00; 137.11; 126.69; 123.37, FTIR (cm^{-1}): 1732; 1540; 1340, Anal. Calcd. for C 43.35; H 1.12; N 15.55; O 39.98. Found: C 43.27; H 1.17; N 15.54; O 39.69%.

2,4,7-Trinitro-9-fluorenone (3)

A solution containing 20.01 g (77 mmol) of 2,7-dinitrofluorenone (**6**) in 75 ml of concentrated sulfuric acid was added dropwise to a mixture of 11 ml concentrated nitric acid and 11 ml concentrated sulfuric acid at 60 °C. During the addition, the heating was gradually increased from 60 °C to 130 °C. At the end of the addition, the mixture was cooled and poured into cold water. After filtration, the yellow solid was washed with water and dried. The solid was purified by recrystallisation from acetic acid yielding yellow needles (57%). Rf: 0.58 (CH_2Cl_2). ^{1}H NMR (200 MHz, δ DMSO d_6): 8.99 (d, J = 1.88 Hz); 8.63 (dd, J = 8.67 and 2.26 Hz); 8.61 (d, J = 1.88 Hz); 8.43 (d, J = 2.26 Hz); 8.19 (d, J = 8.67 Hz), ^{13}C NMR (50 MHz, δ DMSO d_6): 187.18; 150.48; 149.70; 145.60; 144.13; 139.62; 138.65; 136.96; 131.58; 128.78; 126.77; 122.98; 119.79, FTIR (cm^{-1}): 1732; 1542; 1343, Anal. Calcd. for C 49.59; H 1.68; N 13.27; O 35.59. Found: C 49.54; H 1.60; N 13.33; O 35.53%.

4,5-Dibromo-2,7-dinitrofluorenone (7)

77 g (433 mmol) of *N*-bromosuccinimide was added in small portions over 4 hours, with agitation, to a solution containing 15 g (54 mmol) of 2,7-dinitrofluorenone (**6**), 225 ml of trifluoroacetic acid and 90 ml of concentrated sulfuric acid at 65 °C. The mixture was stirred for 24 hours at 65 °C (until the bromine vapour had disappeared). After hydrolysis and filtration, the yellow–orange precipitate formed was washed with water and purified by recrystallisation from acetic acid yielding yellow needles (82%). ^{1}H NMR (200 MHz, δ $CDCl_3$) 8.74 (d, J = 2.07 Hz); 8.59 (d, J = 2.07 Hz), ^{13}C NMR (50 MHz, δ DMSO d_6): 185.43; 149.09; 146.97; 139.19; 136.07; 117.43, FTIR (cm^{-1}): 1730; 1540; 1343; 580, Anal. Calcd. for: C 36.48; H 0.94; N 6.55; Br 37.34; O 18.69. Found: C 36.47; H 0.93; N 6.59; Br 37.39; O 18.58%.

4,5-Dicyano-2,7-dinitrofluorenone (4)

9.56 g (22.3 mmol) of 4,5-dibromo-2,7-dinitrofluorenone (**7**) was dissolved in 100 ml of anhydrous DMF at 80 °C. 6.56 g (73.3 mmol) of copper cyanide was added in portions, and the mixture stirred at 80 °C for 4 hours. A solution containing 35 g (215 mmol) of iron(III) chloride, 150 ml of water and 17 ml of concentrated hydrochloric acid was then added and the mixture was stirred at 70 °C for 3 hours. The mixture was cooled to ambient temperature, filtered and the precipitate was washed with water. Sodium chloride was added, and the aqueous phase was extracted with ethylacetate. The combined organic phases were dried over Na_2SO_4 and concentrated. 500 mg of brown solid was recovered. The precipitate was washed with toluene in a soxhlet. After evaporation of solvent, a further 4.2 g of brown solid was recovered. The brown solids were combined and purified by

Table 5 Crystallographic data

Parameter	7	4	CTC 4/1
Formula	$C_{13}H_4Br_2N_2O_5$	$C_{15}H_4N_4O_5$	$C_{29}H_{16}N_4O_5S$
M	428.00	320.22	532.52
System	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P21/n$	$P21/n$
a/Å	10.3660(2)	14.1690(8)	7.7310(4)
b/Å	16.0720(5)	6.4510(4)	15.1430(9)
c/Å	8.3120(2)	15.2380(11)	21.1520(14)
β/°	103.372(2)	110.614(2)	98.189(2)
V/Å^3	1347.26(6)	1303.64(14)	2451.0(3)
Z	4	4	4
ρ/g cm^{-3}	2.110	1.632	1.443
μ/mm^{-1}	6.043	0.128	0.182
θ range/°	2.38–31.00	2.44–27.69	1.66–24.39
Number reflections measured	14094	5902	13094
Number of independent reflections	4181	2562	3983
R_{int}	0.078	0.049	0.135
Final R value ($I > 2\ \sigma(I)$)	0.063	0.054	0.068
Final R (all data)	0.115	0.090	0.147

column chromatography with dichloromethane to give a brown solid (56%). ^{1}H NMR (200 MHz, δ DMSO d_6): 9.10 (d, J = 2.25 Hz); 8.67 (d, J = 2,18 Hz), ^{13}C NMR (50 MHz, δ DMSO d_6): 185.83; 150.33; 147.32; 138.38; 136.79; 123.32; 116.50; 109.85, FTIR (cm^{-1}): 3063; 2244; 1731; 1530; 1350, Anal. Calcd. for: C 56.26; H 1.26; N 17.50; O 24.98. Found: C 56.13; H 1.25; N 17.50; O 24.94%.

Crystal structure determination

Single crystals suitable for X-ray diffraction were grown from chloroform. The crystallisation a 1 : 1 mixture of **1** and **4** from chloroform resulted in a 1 : 1 molecular complex. Needles were stable in air for several weeks at room temperature. X-Ray diffraction experiments (see Table 5) were carried out on a Kappa CCD Nonius diffractometer using graphite-monochromated MoKα radiation. The intensity data were measured at 295 K. The structures were solved using direct method and refined by full-matrix least-squares on F^2 using SHELXTL.[38]

CCDC reference numbers 253625 (for compound **4**), 253627 (for compound **7**) and 253626 (for **CTC 4/1**). See http://www.rsc.org/suppdata/gc/b5/b502672e/ for crystallographic data in CIF or other electronic format.

Synthesis of Merrifield resin

A 250 mL reactor was charged with 60 g of poly(styrene-co-divinylbenzene) resin (Aldrich 42,698-9) (300–800 μm) and a solution of 185 mL of chloroform and 12.5 g (155 mmol) of chloromethyl-methyl ether[39] at 20 °C. A solution prepared by cautiously adding 8 mL (68.5 mmol) of tin(IV) chloride to 12.5 g (155 mmol) of chloromethyl-methyl ether and 25 mL of chloroform was added dropwise with gentle stirring to the cooled mixture over a 30 min period. After 24 hours at ambient temperature, the resin was collected by filtration and washed successively with dioxan–water (1 : 1), dioxan–water–HCl (5 : 5 : 1), water, dioxan, THF and finally pentane. Anal. Found: C 82.25; H 6.74; Cl 6.69%. The accessible chlorine on the resin was determine by Volhard titration[40] and was found to be 1.37 mmol Cl g^{-1}, FTIR (cm^{-1}): 3017, 2925, 1600, 1510, 1450, 1280, 1120, 610.

Synthesis of resin 10

74 ml (820 mmol) of hydrazine as a 35% weight in water was slowly added to 40 g of chloromethyl resin (1.37 mmol Cl g^{-1}) in 60 ml of ethanol at ambient temperature. At the end of the addition, the mixture was mechanically stirred for 24 hours at 60 °C. The resultant resin was then filtered, washed with water then with ethanol. Anal. Found: C 80.97; H 6.79; N 1.41; Cl 1.86, Accessible chlorine: 0.15 mmol Cl g^{-1} FTIR (cm^{-1}): 3018, 2927, 1608, 1452.

Synthesis of resin 7

5.01 g (14 mmol) of 4,5-dicyano-2,7-dinitrofluorenone (**4**) was dissolved in 650 ml of toluene and 10 ml of acetic acid, then 10 g of resin **10** was added. The mixture was mechanically stirred for 3 days at 75 °C. The resin was then washed for 48 hours with toluene in a soxhlet, then with pentane and was dried at 60 °C yielding brown resins. Anal. Found: C 81.39; H 6.30; N 1.93; Cl 1.86; O 7.75, accessible chlorine: <0.05 mmol Cl g^{-1}.

The loading capacity was calculated based on nitrogen elemental analysis and was found to be 0.4 mmol π-acceptor **4** per g. FTIR (cm^{-1}): 3020, 2925, 1700, 1606, 1540, 1347.

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Cu(II) extraction by supercritical fluid carbon dioxide from a room temperature ionic liquid using fluorinated β-diketones

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Copper(II) can be extracted in supercritical CO_2 from a room temperature ionic liquid using CO_2-philic fluorinated β-diketonate ligands; thanks to the 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($BMIMTf_2N$) ionic liquid properties, there is no need to add modifiers to the neat supercritical CO_2 to reach high extraction efficiencies.

Nowadays, supercirtical carbon dioxide (Sc-CO_2) is considered as a clean technology since the CO_2 phase can be recycled generating almost no waste. Therefore, extraction and waste cleanup applications use Sc-CO_2 as solvent.[1] Fluorinated β-diketonates are the most studied chelates for supercritical fluid extractions (SFE). Transition metals as well as lanthanides and actinides have been extracted by β-diketonates under several conditions in supercritical carbon dioxide from solid or liquid media.[2–6] Tributylphosphate (TBP) is generally used as a CO_2-philic synergist agent to stabilize metal chelates, thus enhancing metal extractions efficiencies. Room temperature ionic liquids (RTILs) are another emerging "green" class of solvents. They are being studied and developed because of their recyclability and their non-conventionnal solvent properties. RTILs are now clearly established as a new family of non-harmful solvents.[7] Many properties such as the solubilization ability, hydrophobicity and hygroscopicity can be fine-tuned, by simply modifying the cation and the anion that form the resulting RTIL. 1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ($BMIMTf_2N$) is one of the most studied RTILs so far. Owing to its Sc-CO_2 solubility properties,[8] $BMIMTf_2N$ seems to be the best solvent from which to perform an efficient metal extraction using Sc-CO_2. In this paper, we have combined RTILs and Sc-CO_2 for metal extraction, and we report the first quantitative extraction of copper from a RTIL phase ($BMIMTf_2N$) into supercriticial CO_2.

$BMIMTf_2N$ synthesis is based on the method developped by Moutiers *et al.*[9] but an optimization of the washing step has been performed. Before the anion exchange, the first step product BMIMCl is washed with ethylacetate. By adding dichloromethane to ethylacetate (30% vol), the final purified batch contains a lowered chloride amount, equal to 12 ppm. After purification, the water content determined by Karl-Fischer titration, is equal to 8100 ppm (0.65 M). Thanks to its moisture stability, $BMIMTf_2N$ was used without a further drying procedure.[10] A structural characterization of $BMIMTf_2N$ has been performed by ^1H and ^{19}F NMR spectroscopy. Data are displayed in Table 1. Copper(II) hexafluoroacetylacetonate hydrate ($Cu(HFA)_2$, Aldrich) or copper(II) trifluoroacetylacetonate hydrate ($Cu(TFA)_2$, Aldrich) and tributylphosphate (TBP, Aldrich 98%) were used as received. Copper concentrations were equal to 10^{-3} M. The copper solutions in $BMIMTf_2N$ present a bright blue–green color characteristic of the hydrated form of the Cu(β-diketones)$_2$ complexes. Upon addition of TBP, the color turns to a very light brown. Cu : complexing moieties : TBP stoichiometries were 1 : 2 : 3.

$$Cu(HFA)_2 \cdot xH_2O + 2TBP \rightarrow Cu(HFA)_2TBP_2 + xH_2O \quad (1)$$

All RTIL/Sc-CO_2 experiments were performed with a lab-built supercritical fluid extraction apparatus that includes a liquid CO_2 tank, a high pressure syringe pump, an extraction cell and a collection vial. SFC-grade CO_2 was supplied with a syringe pump (ISCO, model 260 D, Lincoln, NB). A schematic diagram of the overall experimental apparatus is shown in Fig. 1. All the extraction experiments were performed with a stainless steel high

Table 1 Chemical shifts for ^1H and ^{19}F NMR using D_2O as solvent. The numbered protons refer to the chemical scheme of $BMIMTf_2N$

	Chemical shift (in ppm)							
^1H	H^1 (s)	H^2 (s)	H^{3a} (s)	H^{3b} (s)	H^4 (t)	H^5 (m)	H^6 (m)	H^7 (t)
	3.75	8.43	7.30	7.25	4.02	1.70	1.19	0.75
^{19}F	F : (s) −80.3							

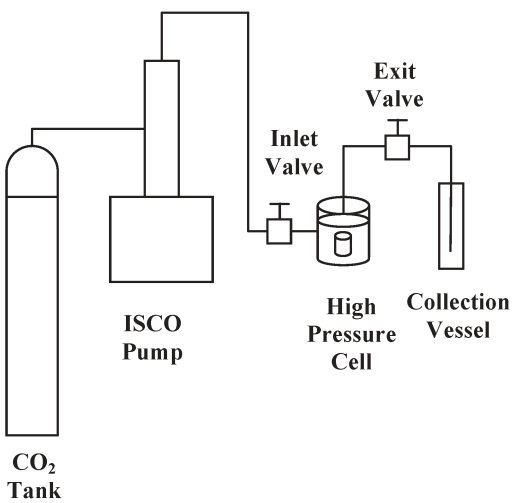

Fig. 1 Schematic diagram of the experimental system used for the Sc-CO_2 extraction from $BMIMTf_2N$.

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pressure extraction vessel (13 ml) maintained at 50 °C by placing it on a heater-plate and thermo-regulated by a stainless steel thermocouple probe (K type) inserted into the cell. Extractions were performed on 1.5 ml aliquot solutions poured into a 3 ml beaker and put into the extractor under stirring conditions. When the extraction cell is set to 50 °C, CO_2 is pressurized to 150 atm. The extraction process is allowed to occur under static supercritical fluid extraction over 10 min. Then, the exit valve is opened and the CO_2 is flushed under dynamic conditions (flow rate equal to 0.5 ml min^{-1} controlled at the Isco pump) over 50 min. Longer static (30 min) and dynamic (2 h) conditions have been tested. As is illustrated in Table 2, extraction coefficients are not modified. The maximum extraction efficiency is thus reached for 10 min/50 min static and dynamic times. When the extraction modus operandi is complete, the system is allowed to slowly depressurize for about 2 h. The RTIL sample is then removed from the cell and analysed. To determine the elemental concentration of copper and chloride in our samples, and because of the difficulty in using standard analytical techniques such as UV-vis (high absorbance of $BMIMTf_2N$) or ICP-AES (impossiblity to make aerosol droplets with the ionic liquid) we used a nondestructive neutron activation analysis (NAA) method. All samples were irradiated at the Nuclear Radiation Center at Washington State University (Pullman, WA) in a 1 MW General Atomic TRIGA Nuclear Reactor at a steady flux of 6×10^{12} neutrons cm^{-2} s^{-1}. After irradiation, the samples were cooled before being counted, until the total activity of the irradiated sample meets security levels. Each sample was counted for a fixed time on a large-volume Ortec Ge(Li) detector with a resolution of about 2.3 keV at the 1332 keV ^{60}Co peak. ^{64}Cu and its specific γ energies ($t^{1/2}$ = 12.7 h, 1345 keV) and ^{38}Cl ($t^{1/2}$ = 37.2 min, 1642 keV) were used for the identification and quantification of copper and chloride. Calibration of the signal was obtained by the measurement of reference RTIL solutions of known concentrations (45 ppm) in the case of copper. A standard solution (ultra pure water, SRM 1549, NIST) was used for chloride (22 ppm). Standard and reference solutions were irradiated and counted with the samples, under identical conditions. The extraction efficiencies were calculated on the basis of the amount of copper measured in the samples before and after the extraction.

Data presented in Table 2 indicate that copper extraction from $BMIMTf_2N$ occurred with high efficiencies. More than 95% extraction efficiencies are obtained using either of the two β-diketones HFA or TFA. The influence of TBP as a synergistic agent is here almost ineffective if we consider the data uncertainty. How do we explain the very close extraction efficiencies observed for both complexes, $Cu(TFA)_2$ or $Cu(HFA)_2$? In fact, Cu : β-diketones complexes have been characterized and their solubility

Table 2 Percent extraction of copper(II) from $BMIMTf_2N$ using supercritical CO_2 at 150 atm and 50 °C

β-Diketone	10 min static 50 min dynamic	30 min static 2 h dynamic
HFA		
No TBP	95.5 ± 1%	95.7 ± 1%
With TBP	95.2 ± 1%	n/a
TFA		
No TBP	95.8 ± 1%	95.4 ± 1%
With TBP	96.8 ± 1%	n/a

in Sc-CO_2 have been studied. Direct solubility of the hydrated $Cu(HFA)_2$ and $Cu(TFA)_2$ in Sc-CO_2 has been determined by Lagalante *et al.*[11] The number of fluorine atoms of the chelating agent is an outstanding parameter to determine its solubility value in supercritical carbon dioxide.[12] The mole fraction solubility for the hydrated specie $Cu(HFA)_2 \cdot H_2O$ in supercritical CO_2 (under 150 atm and 40 °C) is close to 3.2×10^7, while $Cu(TFA)_2$ has a mole fraction solubility close to 3.3×10^6. TFA, which contains only one CF_3 group, is about ten times less soluble in Sc-CO_2 than the hexafluorinated species HFA, characterized by two CF_3 groups. This influence on solubilities is confirmed by the trend observed on fluorinated β-diketonates lanthanides extraction efficiencies when extracted from aqueous or solid phases into Sc-CO_2. Thus, extraction efficiencies are expected to be different in our experiments for HFA and TFA complexed to Cu, which is not the case.

By contrast to what is observed in water/Sc-CO_2 systems, thanks to the RTILs very low volume expansion and undetectable vapor pressure, under supercritical fluid conditions a biphasic system Sc-CO_2/RTILs is observed. Nonetheless, supercritical carbon dioxide is highly soluble in RTILs. The investigation performed by Cadena *et al.*[8] on the Sc-CO_2 solubility in some imidazolium-based RTILs indicates that the anion dominates the interactions with CO_2 molecules and then influences the Sc-CO_2 solubility. Under our particular temperature and pressure conditions (150 atm and 50 °C) the supercritical carbon dioxide extraction capabilities are caracterized by its specific density equal to 0.78 g ml^{-1}.[13,14] Under highly pressurized carbon dioxide, the RTIL's phase is described as a strongly organized liquid. Thus, CO_2 molecules circulate *via* free interstices formed by the cation–anion spatial arrangement. The underlying structure of $BMIMTf_2N$ under supercritical CO_2 phase is favorable for the CO_2 molecules to penetrate easily in the interstices and therefore allows extraction of the CO_2-philic complexes formed by TFA and HFA. In our experiments, copper is complexed by two diketonates moieties. Because of the overall neutral charge of the copper chelate, we suggest that in this new system $BMIMTf_2N$/Sc-CO_2 the metal complexes are poorly coordinated by the ionic liquid phase so that the energy needed to extract the chelated metals is very low. The partitioning coefficients of such moieties between Sc-CO_2 and the ionic liquid are therefore highly enhanced. It has been shown that for f-block elements, the cations and anions constituting the $BMIMTf_2N$ are present in the outer solvation sphere, as in the case of Eu-chloride complexes[15] and tris-ketonate metals.[16] These weak coordinating properties of $BMIMTf_2N$ can be extrapolated to transition metals (Ni, Pb, Mn, Co, Zn, or Cd using fluorinated β-diketones in different stoichiometries) or heavy metals, such as lanthanides or actinides.

The interest of combining RTILs and Sc-CO_2 should be considered from several points of view. Relative high percent extraction of transition metals from aqueous or solid samples were, in most cases, obtained by adding one modifier (methanol, TBP) and/or additional ligands (dithiocarbamate or cyanex) to the CO_2 phase and/or high pressure conditions (*i.e.* 200 atm).[17–19] In our case, addition of TBP to the system has no impact on extraction efficiencies and thus can be considered as useless. The possibility to efficiently extract metals with neat Sc-CO_2 while minimizing the moieties in the system constitutes a major asset for extractive and separative applications. Current experiments on lanthanide

extraction are resulting in similar conclusions and these results will be published separately.

By decreasing the CO_2 pressure above the critical point, extracted species should be recovered, allowing back extraction processes. The overall apparatus used to perform our extraction experiments was not designed to obtain quantitative back extraction of our copper chelates. A complete cycle including extraction and back extraction steps with both RTILs and Sc-CO_2 solvents should be developed, leading to practical solvent recycling.

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Soxhlet-dialysis: a method to recover soluble polymer supported catalysts†

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Soxhlet-dialysis is used to facilitate the recovery and reuse of a PEG-supported titanium-salen catalyst for the asymmetric silylcyanation of benzaldehyde—up to five times without any loss in activity or enantioselectivity.

There is a widespread interest in developing methods to recover homogeneous catalysts, particularly chiral catalysts, from a reaction mixture.[1] The impetus to recover and reuse homogeneous catalysts stems not only from an economic standpoint but also from the need to eliminate contamination of the transition metal catalyst in the product and in the waste streams. The challenge is to recover the catalyst for reuse without any significant loss in its reactivity and selectivity.[2] We report here a simple method that we call soxhlet-dialysis for the recovery of soluble polymer supported catalysts. Using this method, we show that a PEG-supported titanium-salen complex can be recovered and reused for silylcyanation of benzaldehyde at least five times *without any loss of reactivity and enantioselectivity*. When compared with normal dialysis, soxhlet-dialysis minimizes the amount of solvent that is required because of the recycling of the solvent through reflux.

Among the strategies to recycle catalysts, the use of soluble supports to anchor transition-metal complexes has received considerable attention in recent years.[3] The soluble support ensures that the catalyst is in the same phase as the reactants and reagents. Therefore, the reactivity and selectivity of the catalysts anchored on soluble supports can equal that of the unsupported homogeneous analogs; it is a significant advantage over the catalysts supported on insoluble supports.[4] Initial methods to recover the catalyst for recycling were focused on precipitation and filtration of the supported catalyst by reducing the solubility of the support using an appropriate solvent[5] or by changing the temperature.[6] The precipitated catalyst often shows substantially reduced activity and poor recyclability.[2,7] More recent methods focus on retaining the catalyst in solution and separating it from the reactants and products. These methods include the use of liquid–liquid biphasic solvent systems[8] and pressurized-filtration using membranes with nanometer-sized pores.[9]

We have been interested in using dialysis to recover homogeneous polymer-supported catalysts for recycling.[10] Dialysis relies on a concentration gradient across a semi-permeable membrane and the rate of diffusion declines exponentially as the system approaches equilibrium. In order to re-establish the diffusion gradient, the bulk needs to be periodically replaced with fresh solvent.[11] Therefore, using dialysis to recover catalysts would require large amounts of solvent. To address this issue, we developed a simple semi-continuous-flow dialysis set up using a soxhlet extractor where the thimble is replaced with a dialysis bag (Fig. 1a). The dialyzed solution outside the membrane is continuously replaced with fresh solvent from the reflux, thereby maintaining the diffusion gradient. Of particular concern is the stability of dialysis membranes to organic solvents.[9,12] However, we found that commercially available Spectra/Por® regenerated cellulose membranes are stable to most organic solvents over extended periods of time.

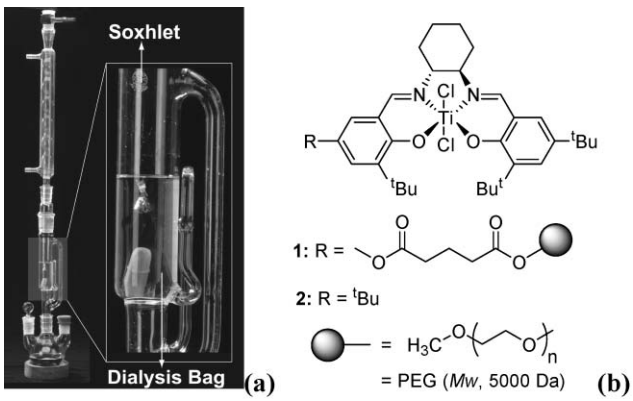
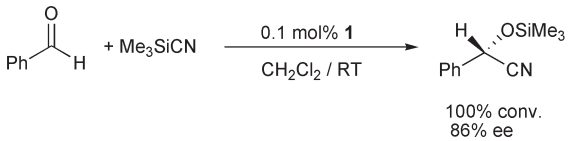


Fig. 1 (a) Soxhlet-dialysis apparatus. (b) PEG-supported Ti-salen catalyst, **1**, and unsupported catalyst, **2**.

We chose the asymmetric silylcyanation of benzaldehyde using a chiral titanium-salen complex as a model reaction.[13] As the soluble polymeric support, we used polyethylene glycol (PEG, M_w = 5000 Da), which was attached to the catalyst through a glutaric acid spacer (Fig. 1b). A solution of the PEG-supported salen ligand[14] in dichloromethane was treated with an equimolar amount of titanium tetrachloride and allowed to stir at room temperature for one hour to give **1**. The solution of the preformed catalyst (0.1 mol% of **1**) was treated with equimolar amounts of benzaldehyde and trimethylsilylcyanide (TMCN) (Scheme 1). The reaction proceeded at room temperature and was monitored by GC until complete conversion (>99%) of benzaldehyde to the product was observed. The product, cyanohydrin trimethylsilyl ether, was obtained in 86% ee after 24 h, similar to the previously reported enantioselectivity achieved with the unsupported catalyst **2**.[13] The reaction was concentrated and placed into a dialysis tubing (molecular weight cut-off = 3.5 kDa) with one end tied shut. A magnetic stir bar was then placed into the dialysis bag to



Scheme 1 Asymmetric silylcyanation of benzaldehyde by **1**.

† Electronic supplementary information (ESI) available: experimental details for the synthesis of the PEG-supported catalyst, characterization data and dialysis/UV-vis experiments for the PEG-dye. See http://www.rsc.org/suppdata/gc/b5/b501826a/

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Table 1 Recovery and change in ee over five runs using **1**

Runs	ee[a] (%)	Conv.[b] (%)	Recovery[c] (%)
1	86	>95	98
2	85	>95	99
3	86	>95	99
4	88	>95	98
5	85	>95	—

[a] Determined by chiral GC using a Cyclosil-B® column. [b] Determined by GC. [c] Determined by GC against a dodecane internal standard. [d] Soxhlet-dialysis was carried out in CH_2Cl_2 at 60 °C using a 3.5 kDa MWCO membrane.

prevent it from floating, and the open end of the tubing was tied shut with a string. The bag was then placed into the soxhlet chamber. Dichloromethane was used as the recovery solvent; 25 mL was placed in the soxhlet chamber, and 100 mL in the three-necked recovery flask. Dodecane was added to the solvent in the recovery flask as an internal standard in order to allow for quantitative GC analysis of the product in the dialysate. The recovery flask was then placed in an oil bath and was heated to 60 °C. The soxhlet chamber refilled every 20 minutes with fresh solvent from the reflux. After 38 h, 98% of the cyanohydrin trimethylsilyl ether was recovered. (Table 1). Changing the capacity of the soxhlet chamber (by changing the size of the soxhlet apparatus) from 25 mL to 100 mL had no effect on the rate of dialysis (see electronic supporting information†).

After each cycle, the contents of the dialysis bag were poured into a round-bottomed flask and treated with fresh benzaldehyde and TMSCN under similar initial reaction conditions; no fresh catalyst was added. Complete conversion to the product was achieved in 24 h. The reaction solution was concentrated and subsequently subjected to another soxhlet-dialysis recovery cycle. The catalyst was recovered and reused for at least five runs without any loss in selectivity or reactivity (84–86% ee, >99% conv.) (Table 1). It is noteworthy that due to the high substrate-to-catalyst ratio for this reaction, recovery of the PEG-supported catalyst by solvent precipitation is impractical.

Even though the catalyst maintained its activity over multiple runs, it was still necessary to assess extent of retention in the dialysis bag. An ICP analysis of the concentrated bulk solvent did not detect the presence of titanium. We then synthesized PEG attached to *p*-methyl-red. A solution of the PEG-dye in dichloromethane was subjected to a soxhlet-dialysis cycle under the same conditions used in the recovery of **1**. Samples of the dialysate were taken over a period of 38 h and analyzed by UV-vis spectrometry. The PEG-dye present in the dialysate was determined to be 3%, reflecting 97% retention in the dialysis bag. Even after 72 h, the amount of PEG-dye retained in the dialysis bag remained constant (Fig. 2). We attribute the initial loss of PEG-dye to low molecular weight polymeric impurities present in the commercially available PEG. Once the low molecular weight impurities are lost, no further loss of the PEG-dye is observed. Based on the differences in the rates of diffusion between the small molecule product and the polymer-supported catalyst, we believe that the retention of the catalyst is much higher than 97%. This is further supported by the fact that no additional catalyst was required for subsequent runs.

In conclusion, we have developed soxhlet-dialysis as a simple and straightforward method for the recovery of soluble polymer-supported catalysts *without any loss in its activity*. This method

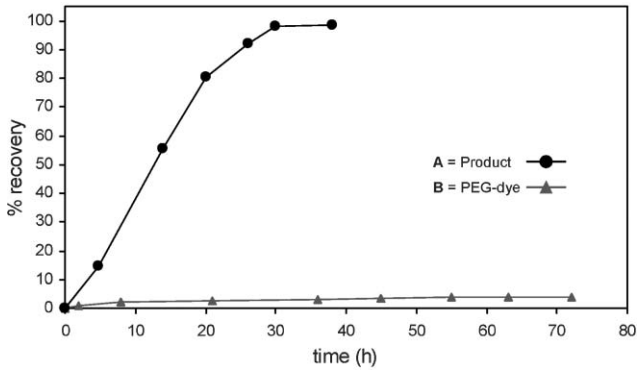

Fig. 2 Retention of PEG-supported catalyst in dialysis bag; (A) recovery of the product cyanohydrin trimethylsilylether (B) recovery of PEG-dye.

employs commercially available dialysis membranes and common laboratory apparatus. Soxhlet-dialysis can be generally applied to recycling of soluble polymer-supported catalysts, without further modification of the original reaction conditions, as well as the purification of soluble macromolecules from low molecular weight impurities.

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Detoxification of malathion a chemical warfare agent analog using oxygen activation at room temperature and pressure

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The organophosphorus insecticide malathion was selected as an analog for the chemical nerve agent, VX. Degradation of 0.44 mM malathion in a 10 mL aqueous solution containing 0.50 g granular zero valent iron (ZVI) under ambient air and pressure was complete after 4 h to the detection limit of GC-FID. The degradation kinetics demonstrate the system to be pseudo-first-order with respect to malathion disappearance with a rate constant of 0.92 h^{-1}. The only non-polar organic intermediates detected were diethyl succinate and malaoxon, of which malaoxon is degraded to below the limit of detection of the GC-FID after 12 h. Electrospray ionization mass spectral analyses show the final reaction products to be low molecular weight carboxylic acids (propionic, oxalic and iminodiacetic acid).

Introduction

There has been heightened interest in the search for an inexpensive, fast, transportable, and environmentally acceptable method for chemical weapon detoxification/destruction after the 1997 Chemical Weapons Convention Treaty and more recently with proliferation fears.[1,2] Currently the most commonly used method for chemical warfare nerve agent detoxification is incineration. Of the known weaponized nerve agents, the V-type or methyl phosphonothioates, such as VX are the most toxic and persistent.[2] This investigation examines a recently discovered room temperature and pressure (RTP) oxygen activation scheme for its ability to destroy malathion, a VX analog. The proposed degradation scheme exhibits the desirable characteristics of green oxidation, *i.e.* environmentally innocuous reagents, solvents and products under mild reaction conditions.

Activation of molecular oxygen is of fundamental importance in catalysis, organic synthesis and biological systems. Monooxygenase systems found in nature, which are capable of efficiently oxidizing organic molecules using activated O_2 under near RTP conditions, include cytochrome P450 and methane monooxygenase (MMO) both of which contain active iron centers.[3] Cytochrome P450 enzymes require reducing equivalents to activate molecular oxygen to a state formally equivalent to that of H_2O_2 during the initial oxidation process.[3] Therefore, peroxides have often been substituted for the reductive activation of O_2 in abiotic studies mimicking cytochrome P450 oxidation.[3] Biological and abiotic systems participating in the partial reduction of molecular oxygen create reactive oxygen species that may consist of superoxide ions and/or hydrogen peroxide. An extremely reactive form of oxygen containing species, $OH^{\bullet}$, is a product of the Fenton reaction (eqn. 1) which is the reduction of H_2O_2 by a suitable iron center.[4]

$$Fe^{II} + H_2O_2 \rightarrow Fe^{III} + OH^- + OH^{\bullet} \quad (1)$$

The hydroxyl radical is a potent oxidizing agent ($E^0 \approx 1.8$ V) and will oxidize almost any available organic at diffusion-limited rates.[4] A system described in a previous publication demonstrates this RTP O_2 activation sequence.[5] This investigation examines the use of **z**ero valent iron, **E**DTA and **a**ir (ZEA) to create radical species *in situ*.[5] The ZEA system is capable of deep oxidation even under mild reaction conditions. There are advantages to using the ZEA system when compared with other systems which have been investigated for the detoxification of organophosphorus compounds such as hydrolysis,[2,6–8] palladium-based catalysis,[9] UV induced photolysis,[10,11] chemical[1,12,13] and enzyme assisted[14–16] oxidation. These include milder reaction conditions, inexpensive reagents, no precious metal catalysts and no need for special pressurized reactors. Additionally, the ZEA reaction proceeds at room temperature under one atmosphere and in aqueous solutions.

The ZEA reaction produces $Fe^{II/III}$EDTA complexes, both of which have a significant role in producing harsh oxidants from dissolved oxygen. For example, the Fe^{II}EDTA complex in oxygenated solutions has been shown to produce the hydroxyl radical.[17] A previous investigation demonstrated that the ZEA reaction was capable of degrading chlorinated phenols to produce low molecular weight carboxylates.[5] This study examines the degradation of malathion [*S*-1,2-bis(ethoxycarbonyl)ethyl *O*,*O*-dimethyl phosphorodithioate] chosen as an analog for VX [*S*-2-(diisopropylamino)ethyl *O*-ethyl methylphosphonothioate] due to the similarities in the phosphorus moiety (Fig. 1).[12,18] Malathion itself is one of the most widely used insecticides in the United States and is unique in its low toxicity to mammals and high toxicity to arthropods.[18] Malaoxon [*S*-1,2-di(ethoxycarbonyl)ethyl *O*,*O*-dimethyl thiophosphate], is a known impurity in technical grade malathion and is far more toxic; LD_{50} (rats) is 12 500 mg kg^{-1} for malathion and 158 mg kg^{-1} for malaoxon.[18] While both malathion and malaoxon irreversibly bind to the enzyme acetylcholinesterase (AChE), inhibiting its control over the central nervous system, malaoxon binding efficiency and therefore toxicity is higher and similar to organophosphorus nerve agents.[10,12,19,20] The proposed ZEA system is capable of oxidizing both malathion and malaoxon to low molecular weight acids. This is a strong indication that the ZEA system can be used in the detoxification of organophosphorus nerve agents such as VX.

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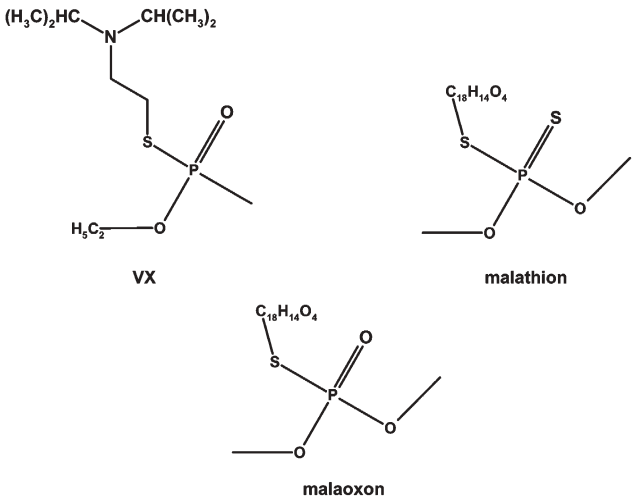

Fig. 1 Structures of VX, malathion and malaoxon show similarities in phosphorus moiety.

Currently there are thousands of tons of VX within the United States alone of which safe and clean detoxification is a major priority and of concern to the general public.[1,12] The ZEA system could be a viable green alternative to current methods of nerve agent detoxification.

Experimental

Iron particles, 0.5 g (40–70 mesh, 99%, Alfa-Aesar, Ward Hill, MA) were added directly to 10 mL of aqueous solution containing 0.44 mM malathion (99.2%, Chem Service, West Chester, PA) and 0.44 mM EDTA (99%+, Acros, Pittsburgh, PA). A pH of 5.5–6.5 was maintained by the reaction mixture without the use of a buffer. This was attributable to the self-buffering nature of the reaction products (organic acids).[5] Therefore, no attempts were made to regulate the pH of these reaction mixtures. Experiments were conducted in 30 mL glass vials at room temperature (20 ± 2 °C), and open to the atmosphere. Small magnetic stir bars were used to stir the reaction mixtures within the glass vials. To obtain decay curves similar to that shown in Fig. 2, 8–15 individual reaction vials were used.

Malathion hydrolyzes at a pH >7 and <5.0, (ref. 21) therefore to achieve high extraction efficiencies the reaction mixture was adjusted to pH 6 using sulfuric acid (Fisher, NJ) and sodium hydroxide (Fisher). After the allotted reaction time, 7 mL of the 10 mL of reaction mixture was removed by pipette, pH adjusted and then diluted to 10 mL. 2 mL of 50 : 50 hexane : ethyl acetate (both Optima grade, Fisher Scientific, Pittsburgh, PA) was added to the diluted 10 mL reaction mixture. The vial containing both the organic and aqueous phase was placed on a rotator for 2 min, at which point the organic layer was removed by pipette and analyzed in triplicate on a GC-FID system (Hewlett-Packard 5890A). Biphenyl (0.60 mM) was present as an internal standard in the hexane–ethyl acetate mixture. All malathion and diethyl succinate concentration measurements were normalized using this internal standard. The malathion extraction efficiency in the presence of 0.44 mM FeEDTA was calculated to be 23% (±2%). Control studies were conducted under N_2 purge, in the absence of ZVI and in the absence of EDTA. All three control experiments resulted in negligible degradation of malathion in 4 hours.

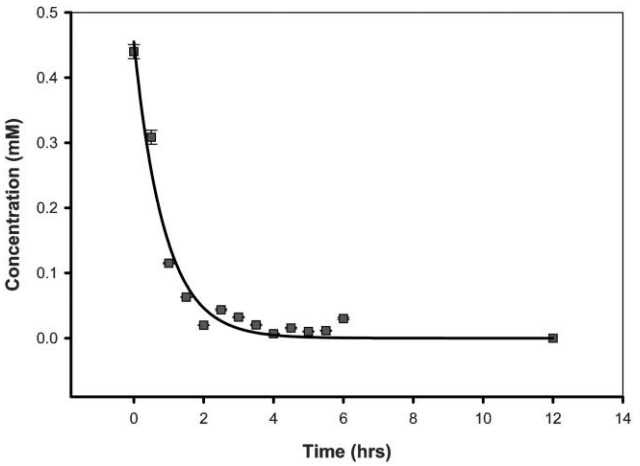

Fig. 2 Malathion degradation profile showing greater than 98% degradation of 0.44 mM malathion within 4 h and degradation to the detection limit of the GC-FID within 12 h. Each data point indicates an individual reaction vial. The error bars represent 1 standard deviation from 3 injections. In most cases the data symbol obscures the error bars.

The GC temperature program used for the analysis of the ethyl acetate–hexane extract had an initial temperature of 60 °C for 1.00 min followed by a ramp of 10 °C min^{-1} to a final temperature of 270 °C for 5 min. The injection port and FID temperatures were 270 and 300 °C, respectively. All injections were performed in splitless mode using helium as a carrier gas at a rate of 3.35 mL min^{-1}. The separation column was an Alltech EC-5 (0.32 mm i.d., 0.25 μm film, and 15 m in length). Mass spectral analyses were conducted on a JEOL JMS-AX505 HA. Ionization was conducted by electron impact with a current of 100 μA. The GC-MS separation conditions were identical to those used in GC-FID.

Nonvolatile aqueous phase reaction products were analyzed using a Micromass Quattro II mass spectrometer equipped with an electrospray ionization probe, two quadrupole analyzers, and a hexapole collision cell. All samples were passed through a 0.4 μm filter and delivered into the source at a flow rate of 5 μL min^{-1} using a syringe pump; analysis was done in both negative and positive ion mode and MS/MS was used for positive identification of peaks. Reference standards were also used for identification of the ESI-MS peaks. Negative ion mode is reported in this work due to the better signal response for the low molecular weight acids. A potential of 2.5 kV was applied to the electrospray needle. The sample cone was kept at an average of 15 V and the counter electrode, skimmer, and RF lens potentials were tuned to maximize the ion beam. Argon was used as a collision gas during daughter analysis. A Dionex System DX-500 ion chromatograph was used to analyze major anions in the reaction mixture, following EPA Method 300.0. Analysis procedures of ions consisted of reference standards, duplicates, and blank measurements.

Control studies were conducted on the ZVI post reaction (4 h). The reaction mixture was centrifuged after 4 h and the aqueous phase decanted. The remaining ZVI was dried with N_2, at which point 2 mL of acetone (ACS grade, Fisher, NJ) was added. After sufficient mixing, the acetone was removed by pipette and analyzed on the GC-FID. This procedure was repeated using

toluene (ACS grade, Fisher, NJ), ethyl acetate (HPLC grade, Fisher, NJ) and 1-butanol (Fisher, NJ). None of extracts showed signs of malathion or intermediate species adsorbed to the iron surface.

The reaction was scaled-up from 10 mL to 3 L (a factor of 300). The overall concentration of malathion (0.44 mM) remained constant, due to this being the maximum solubility in aqueous solution, although the overall mass in the reaction vessel changed from 1.5 mg to 450 mg. The reaction contained 150 g of ZVI, was unbuffered, open to the atmosphere and was stirred using a laboratory mixer (Stir-pak, Cole Parmer Instruments), set at 1500 rpm. The reaction was allowed to react for 19 h. NaCl was added to a point of saturation and 50 mL aliquots of the 3 L reaction mixture was extracted in triplicate with 50 mL of ethyl ether (Fisher, NJ). The ethyl ether was combined (total volume 900 mL) and evaporated *in vacuo*; 25 μL of the pale-yellow oil that remained was transferred to an NMR tube, diluted with 0.8 mL $CDCl_3$ (Aldrich, Milwaukee, WI) and analyzed by ^{31}P NMR and GC-MS. BHT (2,6-di-tert-butyl-*p*-cresol) was used as the internal standard for GC-MS analysis.

All ^{31}P NMR experiments were preformed on a Bruker Advance 500 spectrometer at 202.45 MHz, equipped with a broadband 5 mm probe, operating at +30 °C with H_3PO_4 as external standard. ^{31}P spectra were acquired using 128 000 points and spectra width of 200 ppm. The broadband inverse gated proton decoupling (WALTZ) was used during the acquisition time (1.6 s). Eight scans were acquired with a relaxation delay of 40 s, 128 000 points were used for processing with an exponential window of 1 Hz.

Results and discussion

Fig. 2 shows greater than 98% degradation of 10 mL of 0.44 mM malathion within 4 h and degradation to the detection limit of the GC-FID within 12 h. The kinetics of degradation show the process to be pseudo-first-order with respect to malathion disappearance with an observed rate of 0.92 h^{-1}, from 0 to 4 h. This is strongly correlated with previous studies which examined the degradation rate of 1.1 mM 4-chlorophenol (1.11 h^{-1}) and 0.61 mM pentachlorophenol (0.94 h^{-1}) degradation.[5] The only organic non-polar intermediates present in the malathion degradation were malaoxon and diethyl succinate (DES). The former exhibits a maximum at 4.5 h (Fig. 3). Fig. 3 shows a carbon balance for the malathion carbon, the non-polar intermediate species, DES and malaoxon, from time 0 to 12 h. The total carbon recovered by organic extraction was near 80% except for hours 1–3 and hour 12 of the reaction. During hours one through three, the reaction is believed to contain products that are in a polar form that are non-extractable. At 12 h the reaction mixture contains only 20% extractable organic carbon in the form of diethyl succinate. The other products are polar, low molecular weight carboxylic acids and carbon dioxide as measured in a previous investigation[22] and seen in Fig. 4. Both malaoxon and diethyl succinate increase in concentration to 4 h, after 12 h malaoxon is below the limit of detection for GC-FID while diethyl succinate has a residual concentration of 0.1 mM (20% total carbon).

It is significant that the ZEA system is able to degrade both malathion and malaoxon because both share structural features with VX (see Fig. 1). Direct aqueous injection ESI-MS, Fig. 4, shows the major malathion degradation products after 12 h to be low molecular weight acids (oxalate, propionic, and iminodiacetic acid). Fig. 5 illustrates the proposed degradation scheme for malathion, showing the two non-polar intermediates, malaoxon and DES and the final reaction products as low molecular acids. Iminodiacetic acid has been identified as a degradation product of EDTA and has therefore been left out of the proposed scheme.[22] The phosphorus–carbon and sulfur–carbon bonds of malathion are cleaved during the oxidation process leading to 17% recovery of the sulfur as sulfate and 4.5% recovery of the phosphorus as phosphate after 24 h as examined by ion chromatography. Control studies show no loss of product through adsorption onto the iron surface during the course of the reaction.

A possible use for the ZEA reaction is large scale detoxification of chemical warfare agents. A bench-level reaction scale-up using 450 mg of malathion was conducted. Additionally, this study

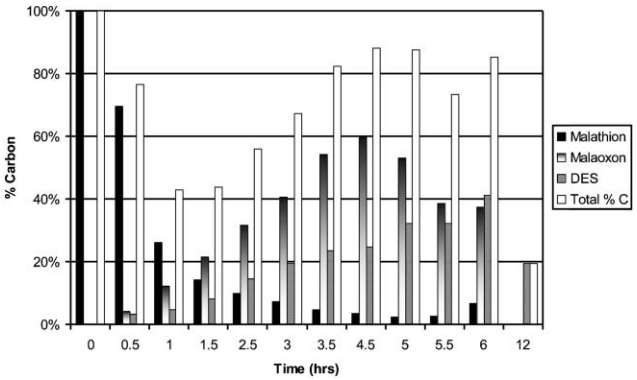

Fig. 3 Carbon balance showing percentage of carbon from malathion present in solution from time 0 to 12 h. GC-FID analysis of 50 : 50 hexane : ethyl acetate extractions of reaction mixture containing 0.44 mM malathion, 0.44 mM EDTA, 0.5 g ZVI.

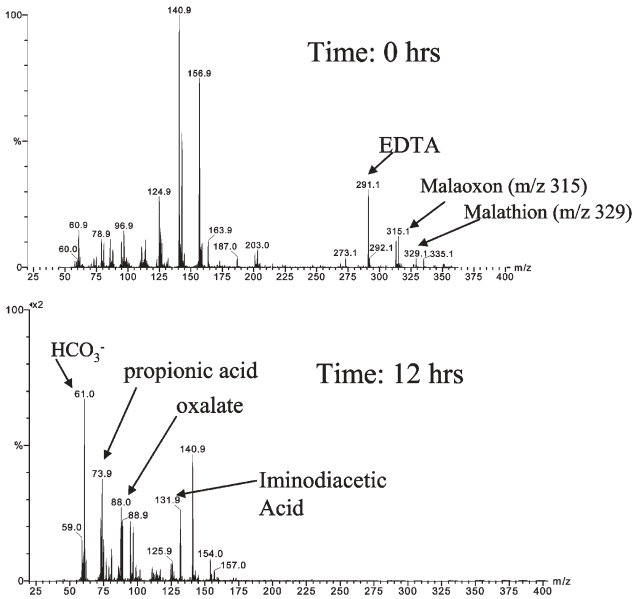

Fig. 4 ESI-MS (negative ion mode) direct aqueous injection of the reaction mixture showing the degradation of both malathion and malaoxon into low molecular weight acids after 12 h. Conditions: 0.44 mM EDTA, 0.5 g granular ZVI, 10 mL total volume, open to the air.

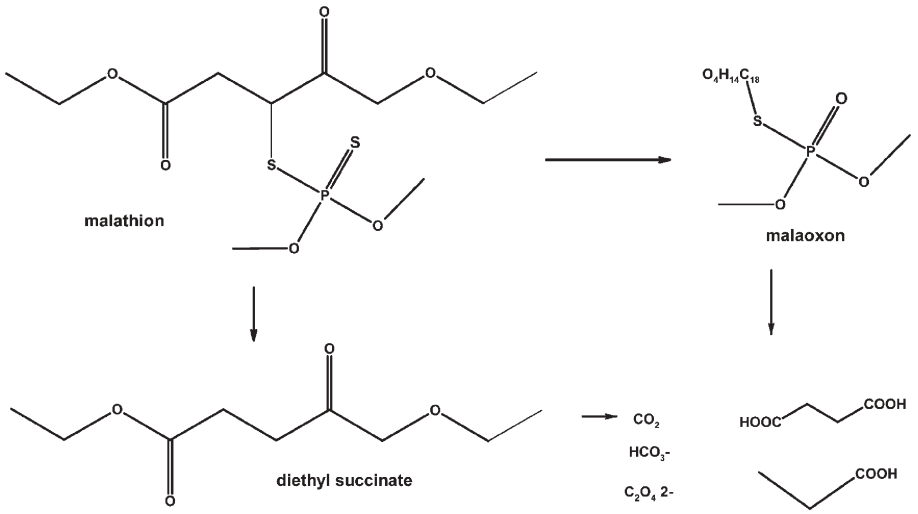

Fig. 5 Malathion degradation scheme showing harsh oxidation of malathion and malaoxon to low molecular weight acids.

allowed for ^{31}P NMR analysis. NMR investigations of this large scale reaction mixture (after 19 h reaction time) revealed two phosphorus peaks, 96.8 ppm and 28.9 ppm. The peak at 96.8 ppm is indicative of phosphorus–sulfur bonds, in malathion. Malathion reference standards verified this shift. The second peak at 28.9 ppm is representative of the phosphorus–oxygen bonds of malaoxon. These were the only non-polar phosphorus containing compounds detected in the ethyl ether extract of the reaction mixture after 19 h. A GC-MS analysis of the same reaction mixture revealed greater than 99% degradation of malathion, indicating the phosphorus peaks in the ^{31}P NMR were representative of small residuals of malathion and malaoxon, representing less than 1% of the original 450 mg. This data further supports the proposed degradation presented in Fig. 5.

The ZEA reaction has advantages over present oxidation technologies. Methods based on chemical oxidants such as bleach or H_2O_2 are attractive, though both have limitations such as long-term storage requirements, or possible safety hazards. For bleach-based oxidations reaction conditions must be properly maintained, *e.g.* VX destruction by bleach requires a sizable excess of HOCl/OCl^- to achieve complete chemical oxidation.[12] Furthermore, the use of copious amounts of chlorine has provoked environmental concerns over carcinogenic chlorinated organic compounds that can be produced, such as those produced in paper production.[1,23] As a green alternative to chlorine based oxidations, H_2O_2 has been examined for VX detoxification. Peroxide activators, such as bicarbonate and molybdate increase the rate of oxidation.[1,12,13] Bicarbonate when added with peroxide forms peroxy anion OOH^- which is capable of selectively oxidizing the phosphorus–sulfur bond.[1] Recent reports of hydrogen peroxide induced chemical oxidations involve using 30 wt% H_2O_2, 0.33 M Na_2CO_3 (to maintain basic pH), and *t*-butyl alcohol as co-solvent to detoxify 10 mM VX in under 1 minute, $t_{1/2}$ = 45 s.[1] The phosphorus–sulfur bond is cleaved to give ethyl methyl phosphonic acid and diisopropylamino ethanesulfonate.[1] Although the products are less toxic, their release may still pose environmental concern. The downsides to using large excesses of highly concentrated H_2O_2 or bleach are the difficulties in transportion, long-term storage, operator safety as well as limited shelf life. The ZEA system would only require the storage of ZVI particles and EDTA, both of which have good stability.

Experiments directly using VX can only be conducted in a limited number of laboratories.[12] However, important insights can be gained by doing work on analog compounds such as malathion.[10] ZEA degradation of malathion has shown the system to be capable of degrading the phosphorus–sulfur groups. Previous studies have shown that the ZEA system is capable of degrading organics down to carbonates, and simple carboxylates.[5] In comparison with other chemical oxidation systems, the ZEA system is able to degrade target xenobiotics in a one-step process without formation of intermediates that may require secondary oxidations.[5,9,10,22] Relative to other systems, another outstanding feature of the ZEA system is the use of mild reaction conditions, *i.e.* room temperature and atmosphere. This characteristic combined with inexpensive and stable reagents, establishes the ZEA system as a strong possibility as a field-portable organophosphorus remediation system.

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New trends in pest control: the search for greener insecticides

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Insecticides have a pivotal role in our lives, not only for crop protection in agriculture, but also to avoid the spreading of harmful pests causing human diseases such as malaria. Due to economic and medical reasons, the design of effective agents that control these pests is quite an important task in agrochemical science and in the industrial sector. Nevertheless, the non-restricted use of highly toxic insecticides for several decades has provoked negative effects in the environment and the poisoning of non-targeted species. For these reasons, the development of selective and harmless insecticides is needed. A short overview of some of the recent advances in the chemistry of insecticides is presented, with a highlight of their greenness compared with classical insecticides. Synthesis, mode of action and environmental profile of pyrethroids, neonicotinoids, and insect growth regulators will be described. Furthermore, the use of biological insecticides such as spinosyns, azadirachtin, and *Bacillus thuringiensis* as green alternatives for synthetic insecticides will also be reviewed.

1. Introduction

The first efficient insecticides were introduced in the middle of the 20th century; before that, pest control was mainly based on the use of inorganic agents such as sulfur, arsenicals, hydrogen cyanide or cryolite,[1] some of which are still being used despite their high toxicity not only for targeted insects, but also for non-targeted species, including vertebrates. The introduction of organochlorine, organophosphorus and carbamate insecticides meant a real revolution[2] in the agrochemical sector, as these compounds have allowed an important minimization of crop losses caused by insect activity.

In this context, the introduction of DDT during World War II as one of the first organochlorine insecticides was remarkable, with a wide spectrum of action and a long residual activity.[3] Nevertheless, a few years later, organochlorine insecticides were shown to cause severe environmental damages, both in terrestrial and aquatic ecosystems.[4] Their persistence provoked an accumulation of organochlorine insecticides in animals through the food chain and as a result, most of these insecticides were banned in many countries,[3] although DDT is still in use in some countries where malaria is endemic.[5] Recent studies suggest that chronic exposure to DDT is associated with neurological impairments,[6] accelerated ageing,[7] and breast cancer.[8]

On the other hand, organophosphorus insecticides, frequently called organophosphates although the term is sometimes chemically incorrect, were developed by Bayer AG[1] in the 1940s, and they proved to be reliable and effective pest control agents. Organophosphorus insecticides affect the nervous system by phosphorylation of acetylcholinesterase,[9] provoking respiratory muscle weakness and neuromuscular dysfunction.[10,11] They are also known to induce tumorigenic risks.[12] The Environmental Protection Agency in the USA (US EPA) is currently reassessing insecticide tolerances;[13] as a result, the US EPA has released an organophosphorus cumulative risk assessment,[14] which resulted in the cancellation[3] of a number of organophosphorus pesticides.

These chemicals, which include some of the most toxic agents still used in agriculture, had a broad spectrum of

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activity against insect pests, and showed only moderate stability in the environment.[3]

Carbamates were developed in the 1950s and are still used today.[3] These insecticides are rapidly detoxified and excreted in warm-blooded animals and, in general, they are selective against targeted insect pests.[15] Nevertheless, carbamates are toxic against some useful insects, such as honeybees. Both organophosphorus and carbamate insecticides act by suppressing the activity of acetylcholinesterase, an enzyme that regulates a neurotransmitter called acetylcholine. Organophosphorus insecticides react irreversibly with acetylcholinesterase, whereas carbamates act reversibly.

Carbamates have a low persistence in soil, plants, and the environment.[3] This, although a positive characteristic from an environmental and human safety point of view, also means that in some cases several applications are needed over a growing season.[3] There is no evidence of carbamates causing delayed neurotoxicity as is found with some of the organophosphorus compounds.[3] Carbamates are not regarded as mutagenic, carcinogenic or teratogenic substances. Several studies[16,17] show an association of long-term carbamate exposure with neuropsychological function impairment, which could be interpreted as evidence of a chronic effect of cumulative high exposure to these compounds. US EPA expects that a preliminary cumulative risk assessment of carbamates will be available by the Spring of 2005.[18]

Apart from these negative environmental aspects, nowadays there are populations of insects which are resistant to organochlorine, organophosphorus and carbamate insecticides.[19] In order to overcome this resistance it would be interesting to have new pesticides with different mechanisms of action.[20]

So, the main goal of pesticide research is the development of new, selective and highly effective substances that cause no harm to human health and the environment.[21] In this article we review the recent advances in the chemistry of insecticides in the search for greener insecticides in terms of environmental toxicity.[22] In this context, compounds such as pyrethroids, neonicotinoids or insect growth regulators will be considered. We will also review the use of biological insecticides such as spinosyns, azadirachtin and *Bacillus thuringiensis* as green alternatives for chemical agents.

2. Pyrethroids

Pyrethroids are synthetic insecticides structurally derived from the six natural pyrethrins,[23,24] isolated from pyrethrum, the plant extracts[25] of *Chrysanthemum cinerariaefolium* flowers. Pyrethrins are esters of a cyclopropanecarboxylic acid (chrysanthemic or pyrethric acid) and a cyclopentenolone (pyrethrolone, cinerolone or jasmolone).[23] For example, pyrethrins I and II (Fig. 1) derive from pyrethrolone and chrysanthemic or pyrethric acid, respectively.

Pyrethrum itself exhibits insecticidal activity[23] against some pests and presents low mammalian toxicity; however, its instability in light and air strongly reduces potential effectiveness. The activity of these compounds is due to their high affinity to insect Na^+-channels, causing neuronal hyperexcitability.[15,26]

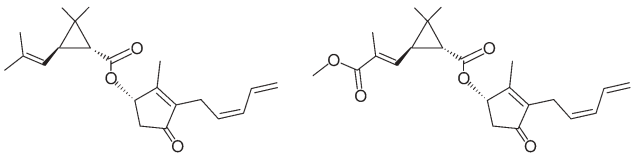


Fig. 1 Pyrethrins I and II.

Subsequent research[24,27,28] meant the replacement of some of the structural elements of pyrethrins. For example, the pentadienyl side chain of pyrethrins I and II was replaced by more accessible moieties with similar steric and electronic behaviour.[23] Different heterocycles were used[28] instead of the cyclopentenolone domain, and an α-cyano substituent in a 3-phenoxybenzyl alcohol moiety[29] was introduced (Fig. 2).

All these structural changes allowed the preparation of a wide range of pyrethroids with improved photostability[23] as compared with pyrethrins. Among these compounds, some important commercially-available insecticides are included, such as tetramethrin and deltamethrin (Fig. 2).[23] Even the substituted-cyclopropanecarboxylic acid moiety was later replaced by an isovaleric acid residue to afford commercial fenvalerate.[23]

These synthetic approaches allowed the development of pyrethroids available not only for indoor uses but also for crop protection and for veterinary and medical pest management.[24]

Bioassays[30,31] revealed that pyrethroids possess a quick knock-down effect against insects and, in general, a low mammalian toxicity.[24] These features, together with a good degree of biodegradability and selectivity, allowed pyrethroids to be considered[24] as the safest, and one of the most effective insecticides at present, with a better environmental profile than organochlorine, organophosphorus and carbamate insecticides. In the last few decades, they have become the second most important group after organophosphorus compounds.[1]

In this context, Table 1 shows the average selectivity between insects and mammals of the most currently used insecticides.[24] As can be seen, pyrethroids exhibit the highest potency against pests, but at the same time show the lowest toxicity towards mammals.[24] Pyrethroid toxicity to humans is

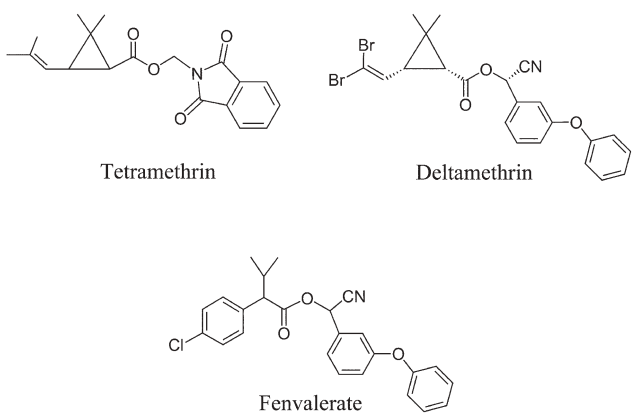


Fig. 2 Commercially-available pyrethroids.

Table 1 Toxicity of insecticides in mammals *vs.* insects

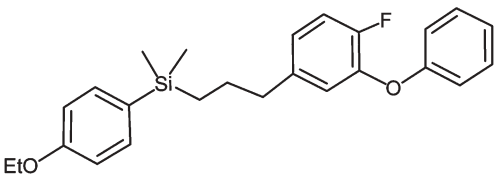
Type of insecticide	Average LD_{50}/μg g^{-1}	
	Mammals[a] (rats)	Insects[a]
Carbamate	45 (15)	2.8 (27)
Organophosphorus	67 (83)	2.0 (50)
Organochlorine	230 (21)	2.6 (26)
Pyrethroid	2000 (11)	0.45 (35)

[a] Number of insecticides tested in parentheses.

at least three orders of magnitude lower than for insects[32] and they are classed as low toxic insecticides for mammals by the World Health Organization.[32] This feature is due to the rapid detoxification in blood and liver carried out by carboxylesterases,[33] the blood half-life of pyrethroids being measured in tenths of an hour.[33] Although pyrethroids are much less toxic for humans than other insecticides, a variety of reversible symptoms such as headache, nausea and cutaneous paresthesia have been reported.[34] Pyrethroids lacking an α-cyano group show the weakest physiological effect and are thought to affect the peripheral nervous system, whereas α-cyano pyrethroids produce symptoms of the central nervous system.[35] Up to now, the US EPA has not released a cumulative risk assessment for pyrethroids.[36]

Nevertheless, several toxicological studies revealed that some pyrethroids are highly toxic to fish,[24] so their use was restricted near water systems. In order to avoid this negative environmental impact, further chemical modifications on the pyrethroid structure were needed.

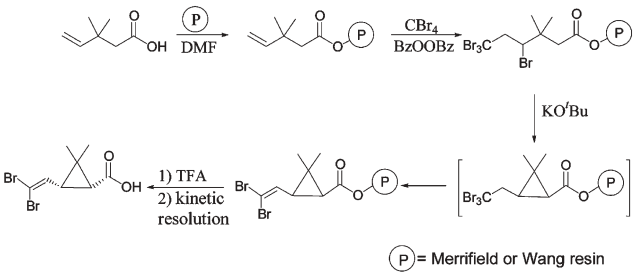
As a result, silafluofen **1**, seemed quite a good substitute,[24] as it showed only negligible fish toxicity (about 10^6 times smaller than deltamethrin), while maintaining high insecticidal activity. This compound includes novel structural features as compared with early pyrethroids, as it lacks the common ester moiety and introduces a quaternary silicon atom in its structure.[37]



1 Silafluofen

Due to the economic and environmental importance of pyrethroids, intense research on these substances is still being carried out.[38–40] In this context, green processes are being developed in terms of selective and non-hazardous procedures of industrial interest for the preparation of pyrethroids. For example, chemoenzymatic syntheses[41,42] are considered, in which one of the key steps is the enzymatic kinetic resolution of enantiomers by using lipases.

Furthermore, radical 1,2-addition of haloalkanes to polymer-bound olefins has successfully been carried out (Scheme 1)[43] in a solid-phase synthesis to afford the dihaloethenylcyclopropane carboxylate moieties present in many pyrethroid-based insecticides.



Scheme 1 Solid-phase synthesis of ciclopropane carboxylate moieties of pyrethroids.

3. Neonicotinoids

(−)-Nicotine and nicotinoids such as (±)-epibatidine (Fig. 3) have been tested as agents in insect control.[44] In particular, (−)-nicotine, obtained from tobacco extracts has been used for centuries as an aphicide in the control of sucking insects, although it has a considerable low potency as insecticide, a narrow spectrum of application and a high toxicity to mammals.

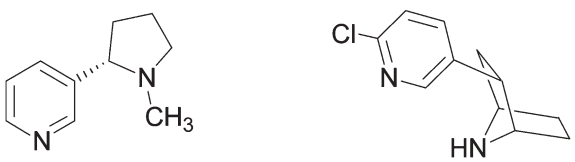
Furthermore, although the insecticidal activity of synthetic nicotinoids has been improved, it has never reached the degree required for commercialization.[44]

Subsequent research led to a novel class of synthetic compounds called neonicotinoids; this term was originally proposed by Yamamoto[45] for compounds having a structural similarity to nicotine and a common mode of action. In general, neonicotinoids possess an electron-withdrawing group, either a nitroimino, cyanoimino or nitromethylene moiety[44,46,47] (Fig. 4).

Both nicotinoids and neonicotinoids are agonists at the nicotinic acetylcholine receptors[20,46,48] (nAChRs); however, nicotinoids are ionized at physiological pH and they are selective for the mammalian nAChRs. On the other hand, neonicotinoids are not ionized under physiological conditions and are selective for the insect nAChRs at a nanomolar level[49] due to differences in the composition of the receptors in insects and vertebrates.[50] This feature provides an excellent example of selective toxicity,[44] with low acute toxicity to mammals, birds and fish, but they display some chronic toxicity in mammals.[51]

It is thought that agonist recognition by insect nAChRs probably involves a cationic subsite of a lysine or arginine moiety[48] for interaction with the nitro or cyano group of neonicotinoids (Fig. 5).

The activity of neonicotinoids contrasts with the action of pyrethroids,[52] which interact with presynaptic sodium



(-)-Nicotine (±)-Epibatidine

Fig. 3 (−)-Nicotine and nicotinoid (±)-epibatidine.

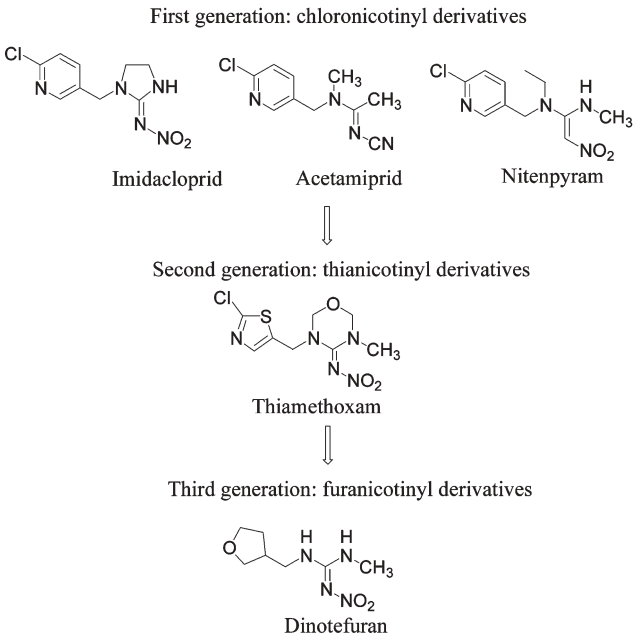


Fig. 4 The three generations of neonicotinoids.

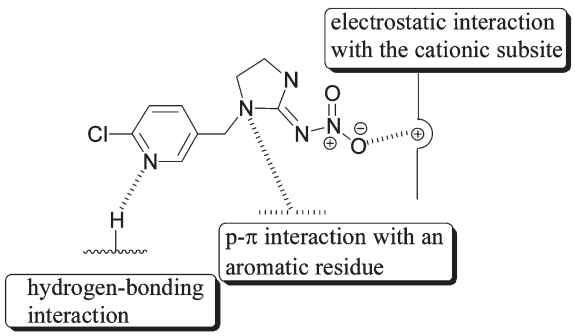


Fig. 5 Interactions of neonicotinoids with insect nicotinic acetylcholine receptors (nAChRs).

channels, and of organophosphorus and carbamate insecticides,[53] which inhibit acetylcholinesterases.

Thus, neonicotinoids represent a new generation of synthetic insecticides as they combine unique properties allowing them to be the fastest growing synthetic insecticides on the market.[54] Some of these unique properties[54] are a broad-spectrum insecticidal activity (especially lethal for sucking and chewing insects), low application rates, a novel mode of action and a favorable safety profile, as well as lacking cross-resistance to other insecticides. As a result, neonicotinoids are increasingly used in crop protection and animal health care[44,50] due to the decrease in effectiveness of organophosphorus and carbamate derivatives, as well as their toxicity to vertebrates.[50]

The first successfully used neonicotinic insecticide was imidacloprid, introduced by Bayer AG and marketed as Admire® in 1991;[55,56] this compound belongs to the first generation of these novel insecticides[57] together with acetamiprid, and nitenpyram (Fig. 4). All of them possess a 6-chloropyridin-3-yl moiety, which was supposed to be necessary for these compounds to exhibit insecticidal activity.

Like many other neonicotinoids, imidacloprid is efficient at low rates and is safe for both human beings and the environment.[46,58] Imidacloprid is at present one of the most effective insecticides, with a level of activity similar to that exhibited by pyrethroids and higher than that of organophosphorus and carbamate derivatives.[20] It is thought that its scale of application will reach that of pyrethroids in just a few years.

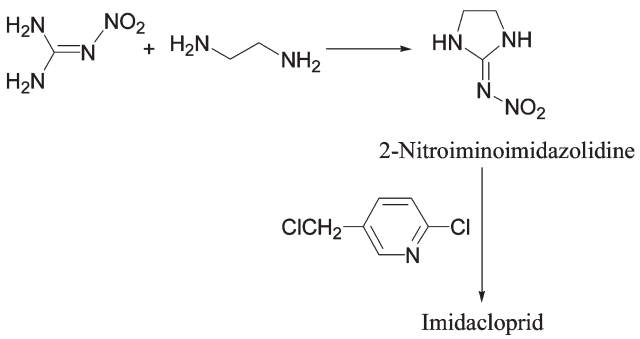
The key step for the preparation of imidacloprid involves the alkylation of 2-nitroiminoimidazolidine[20] with 2-chloro-5-chloromethylpyridine (Scheme 2).

The success of the first generation of neonicotinoids has prompted researchers and the agrochemical industry to investigate a wealth of structural variations of imidacloprid,[46] so as to develop more active and greener insecticides by carrying out structure–activity relationship studies and chemical syntheses.

Research starting from parent structures, such as the tetrahydro-1,3,5-oxadiazine derivative shown in Fig. 6, proved that replacement of the 6-chloropyridin-3-yl moiety by the 2-chlorothiazol-5-yl group (thiamethoxam, Fig. 4)[54] and the addition of a methyl group in the pharmacophore allowed an increase in activity against chewing and sucking insects. This led to the second generation of neonicotinoids, whose major example is thiamethoxam[54,59] (Fig. 4).

Thiamethoxam[60] was first marketed in 1998 for foliar or soil treatment (Actara®) and for seed protection (Cruiser®) against homopteran, coleopteran and some lepidopteran pests. This compound and related structures have low acute dermal and inhalation toxicities[61] and they usually do not provoke allergic reactions either in humans or in animals. It is rated as a likely human carcinogen.[51]

Thiamethoxam can efficiently be obtained by two different synthetic approaches, both starting from *S*-methyl-*N*-nitroisothiourea,[54] and involving the preparation of *N*-substituted-*N*′-nitroguanidine and tetrahydro-1,3,5-oxadiazine intermediates, as shown in Scheme 3.



Scheme 2 Synthetic pathway of imidacloprid from nitroguanidine.

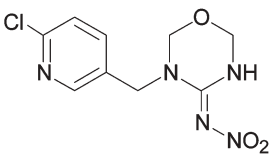
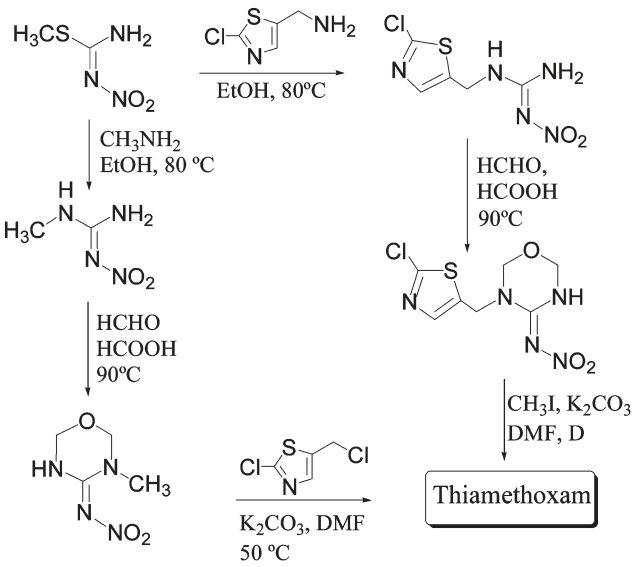


Fig. 6 Parent structure of second generation of neonicotinoids.



Scheme 3 Synthetic pathways of thiamethoxam from *S*-methyl-*N*-nitroisothiourea.

After the commercialization of thiamethoxam, new insecticides with neonicotinoid properties were developed, such as racemic dinotefuran (Fig. 4), marketed under the names Starkle® and Albarin®.[57] This compound could be considered as a member of the third generation of neonicotinoids because of its tetrahydrofuran-3-yl moiety,[57] and it presents one of the best toxicological profiles of neonicotinoids[51] (acute oral LD_{50} value for rats: 2400 mg kg^{-1} and no-observed-adverse-effect-level, NOAEL: 127 mg kg^{-1} d^{-1}).[51]

Nowadays, intense research in this area of agrochemical science still continues, based on synthetic approaches to modified structures,[62–64] quantitative structure–activity relationships[65] and electrophysiological studies.[46] The combination of all these activities will allow a better comprehension of the binding of neonicotinoids[66,67] to the active site of receptors and also the development of new compounds with improved activity and even a better toxicological profile.

Table 2 shows the potency exhibited by some neonicotinoids against some aphids and locusts,[59,66] in comparison with (−)-nicotine. On the other hand, Table 3 shows[48] the difference in binding affinity of neonicotinoids to insect and mammalian receptors.

Table 2 Comparative potency of neonicotinoids and (−)-nicotine

	IC_{50}/nM		
	A. craccivora	*M. persicae*	*L. migratoria*
Imidacloprid	2.3 (±0.8)	3.1 (±0.8)	1.5 (±0.2)
Acetamiprid	4.8 (±2.9)	6.3 (±2.4)	2.9 (±0.2)
(−)-Nicotine	840 (±85)	965 (±280)	320 (±180)

Table 3 Comparative affinity to insect and mammalian receptors

	Housefly LD_{50}/μg g^{-1}	Mouse LD_{50}/μg g^{-1}
Imidacloprid	0.02–0.07	40–50
(−)-Nicotine	>50	6–8

The US EPA has not released a cumulative risk approach in determining pesticide tolerances for neonicotinoids yet.[51] Information regarding human exposure and toxicity is quite rare despite the widespread use of these compounds.[68,69]

4. Spinosyns and spinosoids

Spinosyns are a new class of lactone-derived macrolides with a 21-carbon tetracyclic backbone produced by a culture of the actinomycete *Saccharopolyspora spinosa* as secondary metabolites.[70] They are comprised of a central *as*-indacene-derived core, together with the deoxy sugars D-forosamine and tri-*O*-methyl-L-rhamnose.[71]

These novel compounds were discovered in a soil sample in the Caribbean area in the 1980s as a result of a screening program directed at bacterial metabolites of agricultural and pharmaceutical interest.

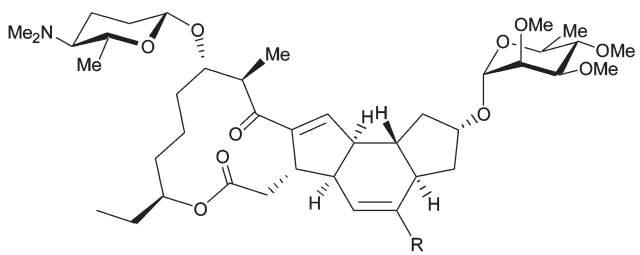
To date, twenty-two naturally occurring spinosyns have been discovered, with different degrees of methylation.[72] It is noteworthy that some other biologically active compounds have been found to have this kind of indacene-derived framework, such as the antibiotics ikarugamycin and capsimycin.[73]

Spinosad is a reduced-risk bioinsecticide[74] registered by Dow AgroSciences in 1997, marketed as Tacer™, and its commercial formulation is a mixture of the natural spinosyns A and D (Fig. 7) in a ratio of about 85 to 15.

Spinosad exhibits extraordinary potency against a broad spectrum of insect pests, especially against lepidopterans and dipterans[75] where its efficiency is sometimes similar to that exhibited by pyrethroids.

The combination of its activity to targeted pests and a better environmental and toxicological profile than most synthetic insect control agents[70,76] makes spinosad a promising insecticide. Spinosad degrades photochemically when exposed to light after application, and strongly adsorbs to most soils, so it does not leach through soil to groundwater. There is no evidence that spinosad is a reproductive toxicant or carcinogen for mammals.[77] No developmental effects were found in either rats or rabbits.[77]

These features have allowed spinosad to be considered as a reduced-risk insecticide by the US EPA.[77] Dow AgroSciences received the US Presidential Green Chemistry Award in 1999 for the development of spinosad.[78]



2 Spinosyn A R = H

3 Spinosyn D R = Me

Fig. 7 Spinosyns A and D.

On the other hand, although spinosyns are sometimes slower to penetrate the insect larvae as compared to pyrethroids, they are not readily metabolized once inside the insect.[70,79]

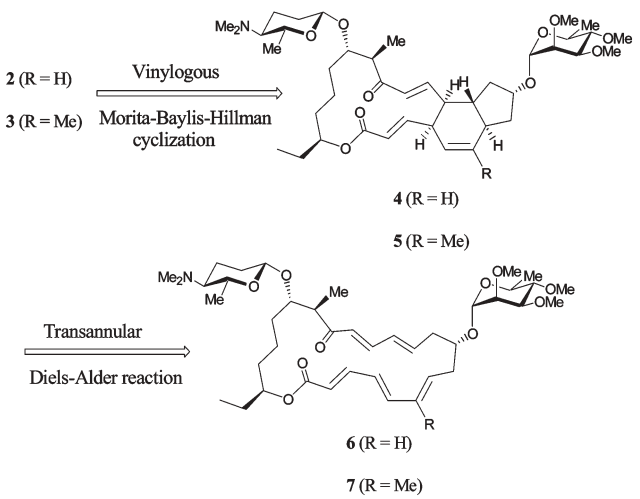
Besides, in a variety of pests, spinosyns are more active[70,79] than organophosphorus and carbamate insecticides, as well as showing a favorable profile for beneficial insect species and low acute mammalian and avian toxicity. Although spinosad is acutely toxic to honeybees under laboratory conditions, field studies reveal that under actual use conditions, the impact on adult honeybees is minimal.[77,80]

Furthermore, spinosyns seem to have a unique mode of action; they show both rapid contact and ingestion activity in insects, an unusual feature for a biological product. Several studies[81–83] suggest that these insecticidal compounds alter both nicotinic and gamma-aminobutyric acid (GABA) receptors, although this interaction does not occur directly through known binding sites, but through an undetermined mechanism. The existence of a novel mode of action is quite important so as to minimize the potential cross-resistance, as compared with classical insecticides.

Evans and Black,[84] Paquette *et al.*[85] and Roush and coworkers[86] reported the first total syntheses of spinosyn A. The search for modified spinosyns has led to the preparation of several hundred synthetic or semi-synthetic derivatives, so called spinosoids.[79,87]

Much effort has been devoted to the synthesis of the tricyclic nucleus of spinosyns or related structures so as to allow access to pure diastereomeric spinosoids.[88] As the biosynthesis[89,90] of spinosyn A is supposed to involve a transannular Diels–Alder reaction and a ring closure of a macrocyclic pentaene, several synthetic approaches are based on these reactions.

For instance, Roush and coworkers have developed the synthesis of the spinosyn tricyclic nucleus in terms of a one-pot tandem intramolecular Diels–Alder reaction and an intramolecular vinylogous Morita–Baylis–Hillman[86,91] cyclization, following the biomimetic strategy shown in Scheme 4. Roush and coworkers have also reported the preparation of the spinosyn nucleus by an Ireland–Claisen ring contraction, followed by an intramolecular Diels–Alder reaction.[92]



Scheme 4 Biomimetic strategy for the synthesis of spinosyn tricyclic nucleus.

Other methods developed to access the indacene-derived core involve chemoenzymatic approaches[93] and oxy-Cope reactions.[94]

In order to improve natural spinosyn production and to obtain a library of spinosyn analogues, genetically modified actinomycetes have been described,[95,96] this process being initiated by Lilly Research Laboratories and Dow AgroSciences. Thus, Gaisser *et al.* have reported[97] the replacement of the β-D-forosamine moiety in spinosyns A and D by L-mycarose (**8**, **9**) and D-glucose (**10**, **11**), using mutant strains of *Saccharopolyspora erythraea* (Fig. 8).

Quantitative structure–activity relationships (QSAR) have successfully been applied in the form of Artificial Neural Networks (ANN)[72,79] to spinosyns and spinosoids in order to determine which structural modifications are likely to improve their insecticidal activity. By this procedure, some spinosoids with greater activity than spinosad against some lepidopteran species have been obtained.[72,79] Fig. 9 shows some spinosoids[72] with more activity than spinosyn A (LC_{50} = 0.31 ppm) against larvae of *Heliothis virescens*, especially in the case of the 2,3,4-tri-*O*-ethyl-L-rhamnopyranosyl **12** and 3-*O*-ethyl-2,4-di-*O*-methyl-L-rhamnopyranosyl **13** derivatives.

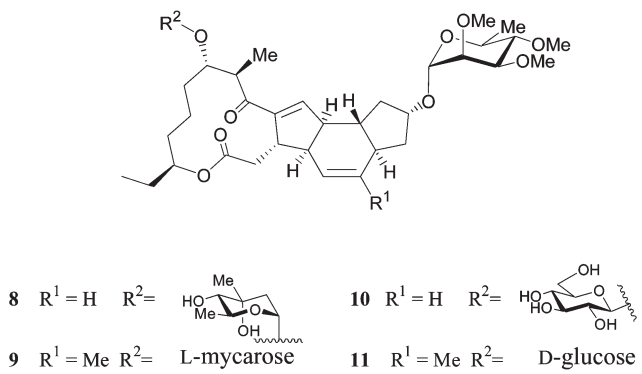


Fig. 8 Spinosyn analogues from genetically-modified actinomycetes.

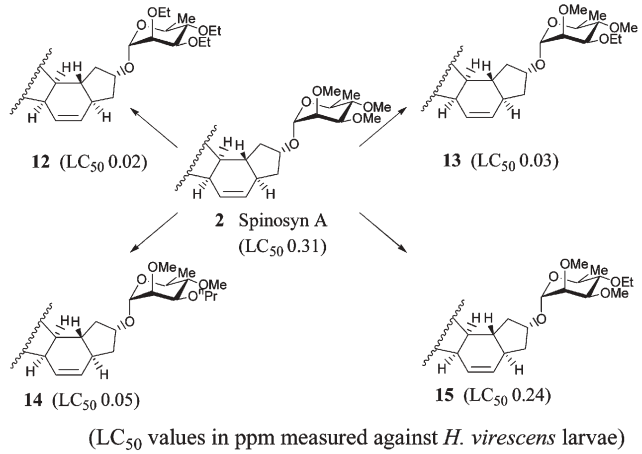


Fig. 9 Biological activity of spinosyn A and analogues.

5. Insect growth regulators (IGRs)

Insect growth regulators (IGRs) are compounds that alter the normal growth process of insects and can therefore be used to control insect populations; these compounds interfere with insect metamorphosis, embryogenesis or reproduction.[98] Among them we find compounds that mimic or antagonise insect juvenile hormone activity and substances that inhibit chitin synthesis in the exoskeleton.[99] Juvenile hormone analogues provoke mortality at adult emergence, whereas chitin synthesis inhibitors cause mortality in larvae and nymphs; besides, both types of IGRs also cause sterilization in adult insects.[100]

The main advantages of these compounds over other insecticidal substances are that they have a low mammalian toxicity and are often very species-specific insecticides;[22,99] nevertheless they usually present a slow mode of action and sometimes a low stability.

5.1. Juvenile hormone-based insecticides

Insect growth is regulated by the action of some hormones such as juvenile hormones (Fig. 10).[22,101] These sesquiterpenoid compounds take part in two important processes: to regulate metamorphosis and the production of eggs in female insects.[102] Due to the specificity of these functions, juvenile hormones have attracted attention[103] as safe and selective targets for the design and development of environmentally friendly and biorational insecticides.[101]

Nevertheless, juvenile hormones (JHs) are usually too unstable to be used as practical insecticides; this feature prompted intense research in order to develop juvenile hormone analogues (JHAs) called juvenoids,[104] either naturally occurring or synthetic, that act by inhibiting the developmental changes associated with embryogenesis, morphogenesis and reproduction. Some JHAs, such as methoprene and hydroprene, are used as commercial household insecticides (Fig. 11);[105] however agricultural use of earlier JHAs has been limited, because of their lack of outdoor stability, their limited insect control spectrum, and their slow toxic action. Both methoprene and hydroprene are now registered by the US EPA. No evidence exists for neurotoxic, oncogenic or reproductive adverse effects in humans that can be attributed to methoprene.[106] Hydroprene was not classified by the US EPA as a human carcinogen.[107]

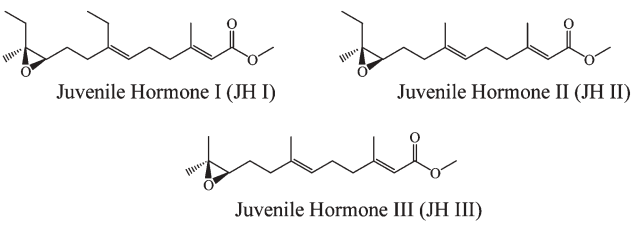


Fig. 10 Juvenile hormones I–III.

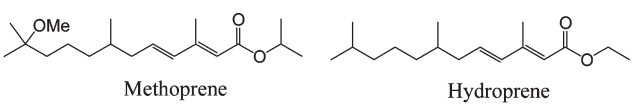
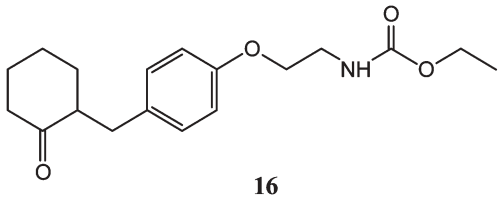


Fig. 11 Juvenile hormone analogues (JHAs).

Esters with juvenile hormone activity were obtained starting from alkenoic or alkadienoic acids and phenoxy- or phenoxyphenoxyethanol.[108] Wimmer *et al.* reported[104] the preparation of racemic cyclohexanone-derived carbamate **16** with JH activity. This juvenoid was more active on the yellow mealworm than natural juvenile hormones I-III.



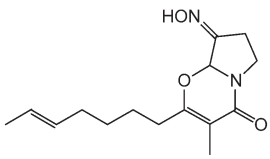
16

The same authors have reported[109] the preparation of esters of the reduced form of **16** by standard acylation of the hydroxy group (Scheme 5). These compounds are considered as juvenogens, that is, agents that liberate during a long period of time the biologically active component (juvenoid) by enzymatic hydrolysis of the ester.[109]

Much effort has also been devoted to the isolation and preparation of compounds that antagonise juvenile hormone activity or that provoke disruption of hormone biosynthetic pathways.[110]

For instance, Primo-Yúfera and coworkers[111] reported the isolation and identification of brevioxime **17**, a metabolite from *Penicillium Brevicompactum*, which exhibits an activity as high as a JH III biosynthesis inhibitor.[110]

The same authors have also isolated[112] the new ketoamide **18** from the same fungus with a high *in vivo* antagonistic JH activity with induction of precocious metamorphosis.



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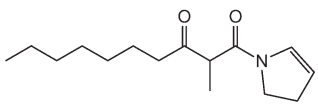
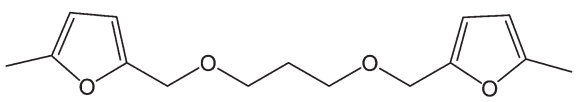


18

Bowers *et al.* have prepared[113] and studied the biological activity of several furanyl-containing ethers such as **19**. These compounds exhibited anti-juvenile hormone activity as evidenced by the induction of premature metamorphosis in some insects.



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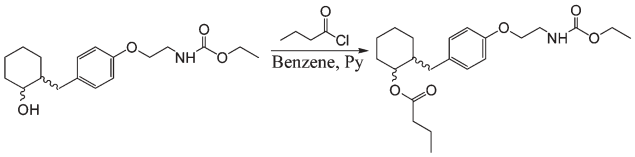
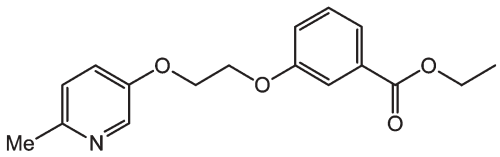


Scheme 5 Synthesis of a juvenogen.

Furthermore, several 6-methyl-3-pyridyl ethers, such as **20**, have been prepared[114,115] and proved to induce precocious metamorphosis of the silkworm *Bombyx mori* when applied to larvae. The presence of the methyl substituent on the pyridine ring was found to be important for its activity.[114]



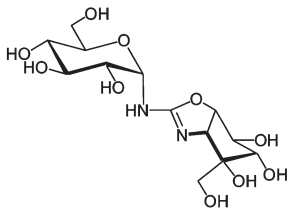
20

5.2. Chitin synthesis inhibitors

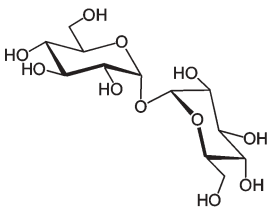
Chitin is a homobiopolymer of *N*-acetylglucosamine (Fig. 12) found in invertebrates, especially in insects and crustaceans, to whom it provides rigidity and serves as a mechanical and protective barrier.[116,117] As chitin is absent from plants and vertebrates, it is considered as a potential and safe target for insect control.[117]

Several natural compounds have been found to strongly inhibit some steps of the biosynthesis of chitin in insects and so they are considered as potential insecticides.[118] For instance, natural trehazolin **21**, an aminocyclitol-derived *N*-substituted cyclic isourea,[119] is a strong *in vitro* inhibitor of trehalase. This is the enzyme required for the hydrolysis[120] of trehalose **22**, the carbohydrate precursor of chitin.[117] The activity shown by trehazolin has prompted its total synthesis and the preparation of structural analogues.[118,121]

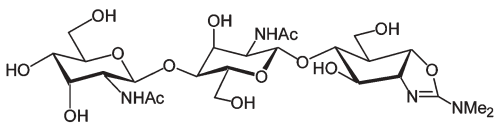
Furthermore, allosamidin **23**, another naturally occurring carbohydrate-derived isourea,[118] shows strong inhibition against chitinase, which plays a pivotal role in the life cycle of insects as it is the enzyme involved in chitin hydrolysis.



21 Trehazolin



22 Trehalose



23 Allosamidin

However, both trehazolin and allosamidin have a large number of hydroxy groups which prevent them penetrating the insect cuticle and reaching their specific targets.[120] This feature has precluded the practical use of trehazolin and allosamidin for *in vivo* pest control.[120]

To date, two different groups of compounds interfering with chitin biosynthesis are used effectively against insects.[117] One group is comprised of nucleoside peptides, such as Nikkomycin-Z[122] (Fig. 13), obtained from a culture of *Streptomyces tendae* and one of the most potent chitin synthase inhibitors. The second group consists of *N*-acyl urea derivatives, such as diflubenzuron[117] (Fig. 13) the first insecticidal benzoylurea marketed almost three decades ago. It presents a high and selective efficiency against lepidopterans at larval stages. Diflubenzuron has been reported to be safe in acute, chronic and genotoxic studies on experimental animals; it is also safe for fish and aquatic invertebrates.[123] Furthermore, diflubenzuron has been shown to exhibit antitumoral effects against several malignant cell lines,[123] and has shown no carcinogenicity after long-term exposure in mice[124] and no teratogenicity in rodents.[125]

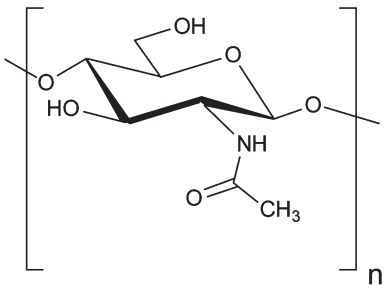
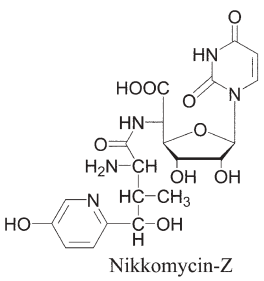


Fig. 12 Chitin structure.

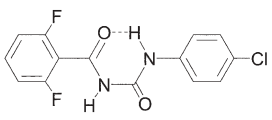
Although the exact action mechanism of acylureas as insecticides has not been proved yet,[126] they act by preventing chitin formation at critical stages in insect life, provoking weakness of the cuticle and disruption in the moulting process.

The interest in acylureas as insecticides has allowed the development of some other commercial ureas, such as hexaflumuron (Fig. 13), which exhibits potent larvicidal activity against termites.[127] This compound, marketed as Sentricon™, received the US EPA registration as a reduced risk pesticide, from environmental and human risk perspectives. It also obtained the 2000 Presidential Green Chemistry Award, presented by the US EPA.[128]

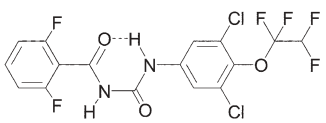
Some other compounds acting on the chitin biological pathway are being tested at present as insecticides. Among them, a novel class of potential insecticides is that of pyridazinone-substituted 1,3,4-oxadiazoles,[98,129] being remarkable in that both oxadiazole- and pyridazinone-derived compounds exhibit insecticidal activity. Thus, oxadiazole containing compounds seem to block the incorporation of



Nikkomycin-Z



Diflubenzuron



Hexaflumuron

Fig. 13 Compounds interfering with chitin biosynthesis.

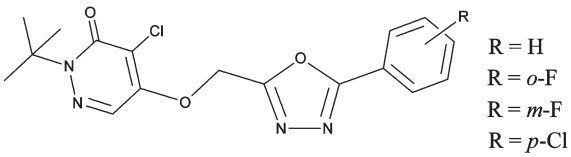


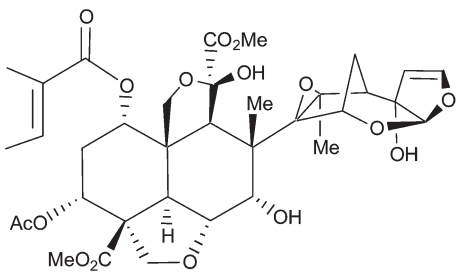
Fig. 14 Compounds with antifeedant activity.

N-acetylglucosamine into chitin biosynthesis,[98] whereas pyridazinone-derived insecticides are found to show juvenile hormone effects.[20]

For instance, compounds shown in Fig. 14 exhibit potent antifeedant activity against larvae of some insects,[98] such as *Pseudaletia separata*, *Pieris rapae*, *Plutella xylostella* and *Bombyx mori*.

6. Neem-based insecticides: azadirachtin

For self-defense purposes, many plants generate chemicals that are toxic to insects. These naturally occurring insecticides are called botanical insecticides or botanicals. They comprise, among others, rotenone, *d*-limonene, sabadilla and ryania, besides pyrethrum and nicotine, described above.[13] However, the most promising botanical insecticide seems to be azadirachtin (**24**), a triterpenoid isolated from the seeds of the Indian neem tree (*Azadirachta indica* A. Juss).[130] For thousands of years, the therapeutic and insecticidal properties of the neem tree have been recognized in India.[130]



24 Azadirachtin

Azadirachtin exhibits insecticidal activity against more than 200 pest species,[131] although only a few of them can be considered as commercial targets because of the relatively high cost of production as compared to synthetic insecticides.[131]

Azadirachtin shows a variety of modes of action. It has been found to be especially active as an antifeedant,[132] and as an insect growth regulator,[132] as it reduces the level of the insect hormone ecdysone. Mating and sexual communications may also be disrupted by azadirachtin, which results in reduced fecundity.[130] These combined modes of action are unique among currently available insecticides.

Azadirachtin is an ideal complementary insecticide in Integrated Pest Management (IPM) programs because it kills phytophagous insects, but has little or no activity against beneficial predatory mites or insects.[131]

This compound is relatively short-lived and easily degradable; furthermore, its mammalian toxicity is low, although it is toxic to fish and aquatic invertebrates.[133] A reversible effect on reproduction of both male and female mammals seems to be the most important toxic effect upon sub-acute or chronic exposure.[134] Nevertheless, risks to human health upon exposure to azadirachtin are not expected when used according to label directions.[134]

Azadirachtin was classified by the US EPA as a biorational insecticide, because of its natural origin and its limited adverse effects on the environment or beneficial organisms.[131]

Because of the great interest in azadirachtin, many synthetic approaches have been reported,[135–140] although its total synthesis has not yet been carried out.

7. Microbial insecticides

Adverse toxicological effects found in many traditional insecticides, together with resistance developed by some pests, have prompted a continuous search for safer substitutes. In this context, the use of living systems as agents for pest control is emerging as a promising area for the future design of environmentally friendly insecticides.[141] Living systems useful in agriculture comprise viruses, bacteria, fungi, insect predators and engineered-plants, microorganisms being the most important ones. Although currently biopesticides only represent about 1% of the world pesticide market, this percentage is expected to increase to 20% by the year 2020.[142] Besides their relative safety to non-targeted organisms, humans and the environment, biopesticides are of great importance in specific IPM programs when produced and delivered correctly.[141]

For instance, in the USA, several baculoviruses, that is, double-stranded DNA viruses, have been registered as pesticides.[143] Baculoviruses are beneficial viruses, as they do not infect man or plants, and provide effective control against many insect species.[144] The use of this kind of microorganism as insecticides presents many attractive advantages, such as a high specificity, adequate pathogenicity, ease of genetic manipulation and minimal residue problems.[143] All the studies conclude[145] that baculoviruses are safe for use as pest control agents against forest pests, as they do not affect non-targeted species; in fact, baculoviruses do not replicate in mammalian cells and they do not seem to be able to enter the mammalian cell nucleus.[146] Nevertheless, the main disadvantages as insecticides[143] are a slow action speed, a too narrow specificity and instability in the environment, as baculoviruses are deactivated by exposure to UV radiation.[147] These factors, together with the difficulty of production and the problems of registration, have limited the use of baculoviruses as commercial insecticides. Biotechnology has allowed the obtention of engineered baculoviruses by insertion or deletions of specific genes, in order to increase their speed of action.[147]

Nevertheless, the most important microorganisms used as biopesticides are bacteria, and especially *Bacillus thuringiensis* (*Bt*), an endospore-forming soil bacterium;[148] in fact, insecticides derived from *Bt* account for 90% of the biopesticide market.[148] There are hundreds of *Bt* subspecies and during sporulation most of them produce one or more insecticidal proteins, so-called δ-endotoxins[149] or insecticidal crystal proteins (ICPs or Cry proteins). Every bacterial strain produces a toxin which is specific against a group of insects;[148] there are currently 150 insect pests that are susceptible to *Bt*.

Cry proteins bind to specific receptors in the larval midgut cells, causing cellular swelling and lysis.[150]

Bacillus thuringiensis-based insecticides have been used since 1961 against caterpillars and more recently, against mosquito and black fly larvae.[151] Commercial *Bt* insecticides are comprised of a mixture of spores, spores undergoing germination, vegetative cells, Cry proteins and cell debris.[151]

The US EPA concluded in 1998 that *Bt*-derived insecticides are eligible for reregistration,[152] as they present a favorable environmental profile. Thus, toxicological studies have concluded that *Bt* is practically non-toxic to humans and mammals[150] (these insecticides are classified as toxicity class III, slightly toxic), and they are safe for most non-targeted species, except for those closely related to the targeted insects. Furthermore, these insecticides do not leach with groundwater and are biodegradable, so they do not persist in the environment.[148]

Nevertheless, δ-endotoxins are readily inactivated, and the number of spores decreases quickly, so several applications are needed in order to keep an effective level of the insecticide.[149] In order to overcome this problem, genetically engineered plants incorporating protectants (PIPs) have been developed to express Cry proteins by incorporating the *Bt* gene.[150] By this approach, the efficiency of pest control is not dependent on application timing and unlike classical pesticides applied to leaves and grass, Cry proteins are present in microgram quantities and are also produced at low levels in the pollen.[150] So, the use of genetically-modified plants as insecticidal agents has allowed an important reduction of chemical insecticides, together with an increase in crop yields by preserving beneficial organisms.[150]

Due to all these advantages, the market of these pest control agents is expected to increase rapidly in the next few years.

Conclusions

The importance of controlling pests has led to the development of a variety of insecticides that prevent agriculture losses and spreading of diseases. Toxicological studies based on acute and chronic effects upon exposure have revealed that many classical insecticides are highly toxic not only to non-targeted insect species, but also to mammals and humans.

Furthermore, some of them, such as several organophosphorus insecticides, have proved to cause cumulative effects on long-term exposure. As a result of more strict regulatory controls issued by the US EPA, the use of many classical insecticides such as organochlorinated hydrocarbons and organophosphorus and carbamate compounds has been restricted or even cancelled.

Consequently, a search for safer alternatives for pest control is needed. Thus, intense research is being carried out to obtain chemically-modified substances with improved insecticidal activity in terms of selectivity towards insects and low toxicity to the environment, and to non-targeted species including humans. The combination of new synthetic approaches and biological and physiological studies has resulted in the preparation of insecticides with a better environmental profile, with different mechanisms of actions, and with reduced risks for living systems. In this context, compounds such as neonicotinoids, pyrethroids or insect growth regulators show a remarkable activity.

However, as a green alternative to synthetic insecticides, biological agents must not be forgotten. So, naturally occurring compounds such as spinosyns and azadirachtin, or living systems such as *Bacillus thuringiensis* have proved to be efficient insecticides against a number of commercially important insect pests. These biopesticides lack the disadvantages present in classical synthetic insecticides; they are considered as low-risk agents, they do not present acute or cumulative risks to humans and are usually quite specific. It is expected that the ratio of marketed biopesticides will increase in the next few years as an attempt to reduce the environmental impact of synthetic insecticides.

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Liquid–liquid behaviour of ionic liquid–1-butanol–water and high pressure CO_2-induced phase changes

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The liquid–liquid equilibrium of the [C_4mim][NTf_2]–1-butanol system presents upper critical solution temperature (UCST) behaviour. We report the influence of added water as well as the effect of hydrostatic pressure on the cloud points. Similarly to previously studied systems that involved RTILs in our laboratories, water is shown to be a very good co-solvent with alcohols. If a small amount of water is present in the [C_4mim][NTf_2]–1-butanol system it decreases the UCST as much as 1.5 K per mol% of water added to butanol. The hydrostatic pressure effect on cloud points is rather modest ($\approx -3.5 \times 10^{-3}$ K bar^{-1}). As for liquid–vapour equilibria, a new apparatus which employs a high-pressure variable-volume cell, was conceived and built. The apparatus was tested for the well-known system 1-butanol–CO_2. Demixing pressures of the ternary and quaternary mixtures, (1-butanol–water–CO_2) and ([C_4mim][NTf_2]–1-butanol–water–CO_2), were determined for a few compositions and temperatures. The demixing pressure is strongly controlled by the water concentration.

Introduction

Over the last decade, environmental chemists have focused their attention on coupling traditional and alternative green solvents in order to design benign media for a cleaner chemistry and sustainable technology. The successful use of room temperature ionic liquids (RTILs) as solvents has been demonstrated for a wide range of organic reactions including acid catalyzed and transition metal catalyzed transformations.[1]

Previous works[2–4] demonstrated that the addition of water to mixtures of RTILs–alcohol markedly increases mutual solubility (co-solvent effect). The ratio of water to alcohol content can be profitably used as a tool for fine-tuning desired situations of total miscibility, partial miscibility, or almost complete phase separation. In contrast, pressurized carbon dioxide (CO_2) acts as an anti-solvent[5] for the ternary RTIL–ethanol–water mixture. Thus, several switches in the number of phases are possible, allowing for reactions to be carried out in a single phase, leading to increased rates as well as catalyst immobilization, and, at a later stage, easy product separation produced by biphasic conditions.

Although RTILs are generally considered as environmentally acceptable media, the subsequent product recovery using additional traditional volatile and flammable molecular organic solvents would reduce the green nature of processes involving ionic liquids. Thus, supercritical carbon dioxide ($scCO_2$) can alternatively be used to extract reaction products. Recent advances in the implementation of the concept of combining these two completely different solvents have been reported.[6]

First, Blanchard *et al.*[7] reported that mixtures of $scCO_2$ with an ionic liquid show gas–liquid equilibrium behaviour whereby carbon dioxide can dissolve significantly into the IL-rich liquid phase, but, in practice, no ionic liquid dissolves in the gas phase. The latter corresponds to a quite different situation as compared to the solubility of common organic solvents in $scCO_2$. The same group has also shown[8] that organic compounds can be extracted from RTILs using $scCO_2$. Based on these principles, researchers have successfully extracted organic compounds from RTILs.[9–11] The type of phase behaviour of RTIL–organics–supercritical carbon dioxide mixtures is, in fact, the same as for systems already observed fifty years ago by Francis,[12] who gave an extensive account of the phase behaviour of binary and ternary mixtures containing carbon dioxide. A number of systems that initially are completely miscible and are separated into two liquid phases by addition of CO_2 were presented. Moreover, the same effect has been observed by Niehaus *et al.*[13]

Knowledge of the phase behaviour of binary and ternary mixtures containing RTILs is absolutely essential for the design of any process involving either chemical reactions or separations in RTIL media. Therefore, it is not surprising that in recent years scientific efforts have been made aiming at understanding the underlying factors that dictate the phase behaviour of RTIL–CO_2 mixtures.[7,14] In order to understand the nature of the interactions of RTIL–CO_2 systems, Kazarian *et al.*[15] reported a molecular-level insight of the state of CO_2 dissolved in ionic liquids using *in situ* ATR-IR spectroscopy. They found evidence for a weak Lewis acid–base interaction between CO_2 and the anions of RTILs, concluding that it is the anion that dominates the interactions with CO_2.

Despite all these studies, there is a serious lack of solubility data for RTIL–CO_2 systems. Therefore, information on ternary mixtures, which is paramount for the design of any technological process, is even scarcer. Few communications on this matter have so far been published. For instance, the T, p, x phase behaviour of the [C_4mim][PF_6]–methanol–CO_2 mixture

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was reported[9,16] as well as phase behaviour of the [C_4mim][BF_4]–water–CO_2 mixture.[17] It was also shown that CO_2 can extract water from various RTILs without dissolution of the latter in the CO_2-rich phase.[18,19] Recently, the solubilities of [C_4mim][PF_6] and [C_4mim][BF_4] in scCO_2 with and without organics were presented.[20,21] Our group[5] demonstrated that it is possible to separate [C_4mim][PF_6] from water–ethanol mixtures using CO_2. As carbon dioxide is added to [C_4mim][PF_6]–ethanol–water, a third phase starts to form between the liquid and the gas phase.

Therefore, only [C_4mim][PF_6] or [C_4mim][BF_4] in combination with organics and/or water and supercritical CO_2, have so far been studied. Since it was proven that these RTILs are potentially harmful[2,22] the scientific community has, more recently, refocused its attention to ionic liquids that do not undergo hydrolysis.[23] For this reason, in this work, we focus our interest on [C_4mim][NTf_2].

In this work, the liquid–liquid phase diagram of [C_4mim][NTf_2]–1-butanol as well as the effect of water added to the same system on the cloud points have been determined using either an already existing[24] He–Ne light scattering apparatus or visual determinations. The influence of pressure on the cloud point has been determined for two compositions.

For vapour–liquid equilibria, a new apparatus, which employs a high-pressure stainless steel variable-volume cell for the determination of cloud points, has been designed, built, and tested. Aiming at testing the method and apparatus, the 1-butanol–CO_2 system has been chosen as it is already well known and has been studied by several authors.[25] Subsequently, the phase behaviour of the quaternary [C_4mim][NTf_2]–1-butanol–water–CO_2 system was studied at different temperatures, pressures, and overall compositions.

Experimental

Materials

[C_4mim][NTf_2] was prepared according to reported procedures[26] and purified at the Department of Chemistry, Universidade Nova de Lisboa. Its purity (estimated at 99.8%) was checked using NMR spectroscopy. Immediately prior to experiments, samples of [C_4mim][NTf_2] were dried under vacuum (0.1 Pa) at moderate temperature (60 °C) for several days. 1-Butanol (purity better than 99.0%) was purchased from Merck and was further dried with 3 Å molecular sieves. Water was distilled and deionized using a Milli-Q water filtration system from Millipore. All liquid solutions were gravimetrically prepared with an estimated uncertainty of 0.05% for a typical non-diluted weight percentage. Carbon dioxide (CO_2) of minimum purity 99.99% was obtained from Air Liquide and was used without further purification.

Experimental apparatus

Since this work deals with both liquid–liquid and vapour–liquid equilibria, different apparatus have been employed. In the case of liquid–liquid equilibrium measurements, both a naked eye technique and a laser light scattering technique have been used. In the case of vapour–liquid equilibrium measurements, a new apparatus which employs a high-pressure variable-volume cell has been designed, built and tested (see below).

Liquid–liquid equilibria. Cloud points at approximately atmospheric pressure for [C_4mim][NTf_2]–1-butanol and/or water mixtures contained in sealed glass ampoules were visually detected based on solution turbidity. All ampoules contained magnetic stirrers for proper mixing. After preparation of the mixtures (gravimetrically), the samples in initially opened ampoules were frozen and vacuum was applied for approximately 5 minutes. Ampoules were then flame sealed and placed in a temperature-controlled bath. Since the above-mentioned mixtures present UCST behaviour, the temperature of the bath was initially raised 2 to 5 K above the expected cloud point (homogeneous region). The sample was then stirred and the temperature was slowly reduced until a cloud point was observed. The estimated precision of the cloud point temperature is within ± 1 K.

The influence of pressure on the cloud points was obtained by a He–Ne laser light scattering technique using an apparatus which operates up to 50 bar. It consists of a thick-walled Pyrex glass tube cell (internal volume $\approx$ 1.0 cm^3, optical length $\approx$ 2.6 mm) connected to a pressurization line with a mercury plug acting as a buffer. The apparatus, as well as the methodology used for the determination of phase transitions have recently been described in detail.[24] The cloud-point temperature accuracy is typically ± 0.01 K in the range $240 < T/K < 400$ while for pressure, accuracy is ± 0.1 bar up to 50 bar.

Vapour–liquid equilibria. The apparatus containing a high-pressure stainless steel variable-volume cell for the determination of cloud points is presented in Fig. 1. The cell (1), of ½ inch internal diameter and *c.a.* 24 ml of total capacity, can operate at pressures up to 1000 bar. The cell was adapted from an original pressure generator (HIP, model 50–6–15). All parts of the pressure generator were kept except for the body that was built as a new piece. The cell has a manually movable piston (2) fitted with Teflon O-rings (3), allowing for the generation of pressure. The entrance (4) of the cell is connected to a stainless steel HIP cross. This enables one to further branch the line, leading to the entrance of carbon dioxide (5) through valve (6), vacuum line (7) through valve (8) as well as to the pressure transducer (9) (OMEGADYNE PX01S1–20KGI). The transducer was calibrated against a Bourdon tube pressure gauge (Heise model CMM). The estimated precision of the pressure determination is ± 0.7 bar. The second entrance (10) permits one to inject the liquid sample into the cell. To this end, a Hamilton syringe coupled with a needle that has a suitable fitting was used. A magnetic stirrer (11) powered by an immersible magnetic plate (12) is placed at the bottom of the cell. The cell is fitted with two thick and flat sapphire windows (not illustrated in Fig. 1), from where a He–Ne laser light (632.8 nm) passes through. The temperature control of the water bath (13) (approximately 80 litres of total capacity) was made by using a Hart Scientific temperature controller (14) (model 2100), with a stability of ± 0.005 °C to ± 0.02 °C. This controller uses a RTD probe (15) from the

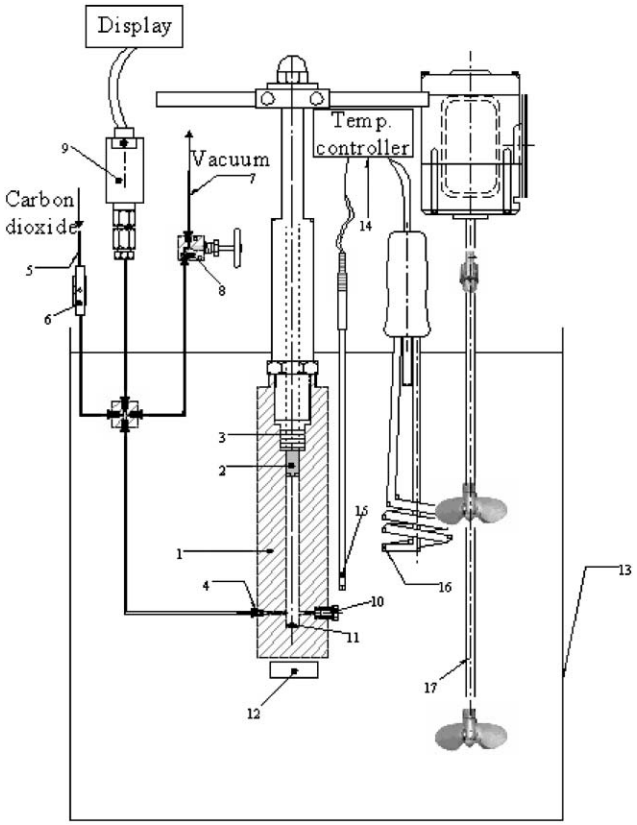

Fig. 1 New apparatus for solubility measurements: (1)–cell, (2)–piston, (3)–Teflon O-ring, (4) and (10)–cell inlets, (5)–CO_2 inlet, (6)–valve, (7)–vacuum line, (8)–valve, (9)–pressure transducer, (11)–magnetic stirrer, (12)–magnetic plate, (13)–bath, (14)–temp.controller, (15)–RTD probe, (16)–heater, and (17)–stirrer.

same supplier (model 2622) as well as a heater (16). The controller and the probe were calibrated against a previously calibrated 4-wire PRT probe. The estimated temperature uncertainty is ± 0.1 K. In order to ensure a uniform bath temperature, a high-power stirrer (17) was used. The whole apparatus is held using a supporting structure, in such a way that all parts of the apparatus are fixed while the bath is placed on a lift-table. This permits us to move the bath up and down.

The cloud-point stage corresponds to a sudden decrease of the transmitted light. It is defined as the pressure, at a given temperature, at which incipient phase separation occurs. At that moment, the solution loses its transparency and becomes turbid. The optical path was designed in a similar manner to that proposed by Rebelo *et al.*[27] An inlet optical cable guides the light from the laser (He–Ne laser light 632.8 nm) to the cell through sapphire windows. The dimensions of both sapphire windows are 14 mm, and 8 mm, for the diameter and thickness, respectively. One terminal of the outlet cable receives the transmitted light through the cell, the other one is connected to a photodiode. The latter converts light intensity into voltage, enabling one to monitor the intensity of the transmitted light.

Each cloud point is determined in accordance with the following procedure: first, vacuum is applied for at least 2 hours and then the piston of the cell is fixed and a known amount of liquid sample is loaded into the cell. The cell is then filled with CO_2 up to the desired initial pressure. The mass of CO_2 that entered the cell can be estimated by knowing the available volume for CO_2 (the volume of the cell minus that of the loaded liquid content) as well as the initial pressure and temperature. In this way we neglect that some gas may have dissolved before recording pressure. Taking into consideration that the time required to charge the gas is relatively short, the associated error is probably very small. The volume of the cell at several marked positions of the piston was previously calibrated based on the ideal-gas expansion of nitrogen at room temperature. The density of CO_2 was calculated using its equation of state.[28] The uncertainty in density resulting from the uncertainty in the measurement of pressure (± 0.7 bar) varied with the pressure and temperature conditions. The error bar in the calculated composition of the mixture had a maximum value of ± 0.04 mole fraction of CO_2.

In contrast to the phase behaviour of the CO_2–1-butanol mixture, systems of high pressure carbon dioxide and room temperature ionic liquids show two distinct phases, even up to very high pressures.[7] Therefore, in the case of CO_2–1-butanol and/or water, the objective is to determine the transition from one to two-phase regions, while in the case of the RTIL–1-butanol–water–CO_2 systems the aim is to detect the formation of the third phase, which precipitates from the upper CO_2-rich phase. Consequently, it is clear why the experimental procedure for detecting cloud points has to be different, mainly with respect to the loading of samples. This is presented in Fig. 2.

The experimental procedure for CO_2–1-butanol and/or water systems uses the following steps (Fig. 2A): the piston is fixed in such a position as to provide the minimum volume of the cell; 1-butanol and/or water as well as CO_2 are loaded into the cell. At this stage, the system is in the one-phase region and slow depressurization can take place, as described in the next paragraph. On the contrary, the method used in the case of mixtures which besides other components contain RTILs, consists of the following steps (Fig. 2B): the piston is fixed in a position that ensures the maximum volume of the cell; the liquid sample is placed into the cell and CO_2 is introduced up to the desired pressure, all together forming three phases; after closing the cell, the piston is moved down (pressure increases) in order to bring the system to the two-phase region.

The cell is immersed into the controlled-temperature bath and heated up to a chosen temperature. The solution is stirred in order to homogenize the mixture and achieve dissolution. At this point, stirring is stopped and pressure is slowly decreased/increased by moving the piston. This is done until a cloud

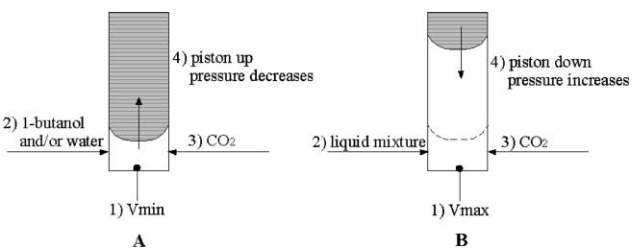

Fig. 2 Experimental procedure for (A) CO_2–1-butanol and/or water; (B) RTIL–1-butanol–water–CO_2. The numbers 1), 2)… represent the chronological order of the experimental operations.

point is obtained, meaning that the two-phase region is observed. Changes in the pressure and intensity of transmitted light are recorded.

Results and discussion

Liquid–liquid equilibrium of [C_4mim][NTf_2]–1-butanol–water mixtures

Fig. 3 illustrates the atmospheric pressure phase diagrams of the [C_4mim][NTf_2]–1-butanol system in terms of IL mass fraction. This system presents upper critical solution temperature (UCST) behaviour, similar to other systems which involve RTILs and alcohols as solvents.[2,3,29,30] Our results have been compared with the data reported by Crosthwaite *et al.*[30] (also presented in Fig. 3). To rationalize the data with the aim of permitting interpolation or extrapolation of the phase diagrams and approximate determination of the critical coordinates, T_c; w_c, a scaling-type equation,

$$|w - w_c| = A\left(\frac{T_c - T}{T_c}\right)^{\beta} \quad (1)$$

has been applied to our experimental cloud points. A and β are merely fitting parameters with no claim to represent critical amplitude and exponent, respectively. The curve shown in Fig. 3 has been drawn using this equation. The insert in Fig. 3 depicts the T–x diagram using IL mole fraction as the field variable. The parameters for a nominal pressure of 1 bar are: critical temperature, T_c = 299.2 K; critical composition, w_c = 0.45; exponent, β = 0.276; amplitude, A = 0.841. The critical composition in weight fraction (w_c) of 0.45 corresponds to 0.13 in mole fraction (x_c) of [C_4mim][NTf_2]. The A and β parameters should be considered as mere fitting parameters without any significance in terms of critical phenomena. As can be observed in Fig. 3, there is reasonable agreement between our experimental results and data taken from the literature[30] (maximum difference in temperature is about 0.8 K).

The coordinates of all experimental cloud points of this system, [C_4mim][NTf_2]–1-butanol and/or water, are reported in Table 1. The influence of pressure on the cloud points (demixing temperatures) has been obtained for two concentrations of the binary [C_4mim][NTf_2]–1-butanol mixture and one concentration of the ternary [C_4mim][NTf_2]–1-butanol–water. All these mixtures show a small pressure effect.

In many ways, the mixture [C_4mim][NTf_2]–1-butanol and/or water demonstrates behaviour similar to other studied mixtures which involve RTILs, alcohols and/or water. Besides the UCST behaviour and asymmetry of the phase diagram when plotted on a mole fraction basis, there is a significant water–1-butanol co-solvent effect. Similarly to the cases of [C_4mim][PF_6]–ethanol[2,3] and [C_4mim][NTf_2]–i-butanol[3] (T_c = 303.5 K; w_c = 0.43; β = 0.257; A = 1.010) mixtures, there is a sharp drop in the demixing temperature as water is added to the [C_4mim][NTf_2]–alcohol mixture (Fig. 4). This

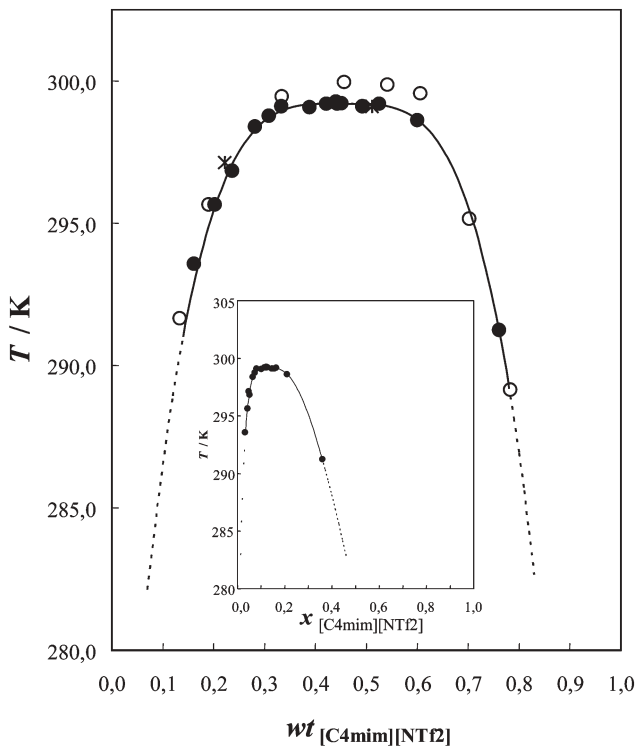

Fig. 3 Atmospheric pressure liquid–liquid equilibrium diagram of ([C_4mim][NTf_2]–1-butanol), where *wt* represents mass fraction. This work: ● (visually detected); * (laser light scattering technique). ○ Crosthwaite *et al.*[30] The insert shows the same diagram using a different variable—mole fraction of [C_4mim][NTf_2]. The solid lines represent the fit to experimental data using the scaling-type eqn. (1) while the dashed lines represent extrapolation.

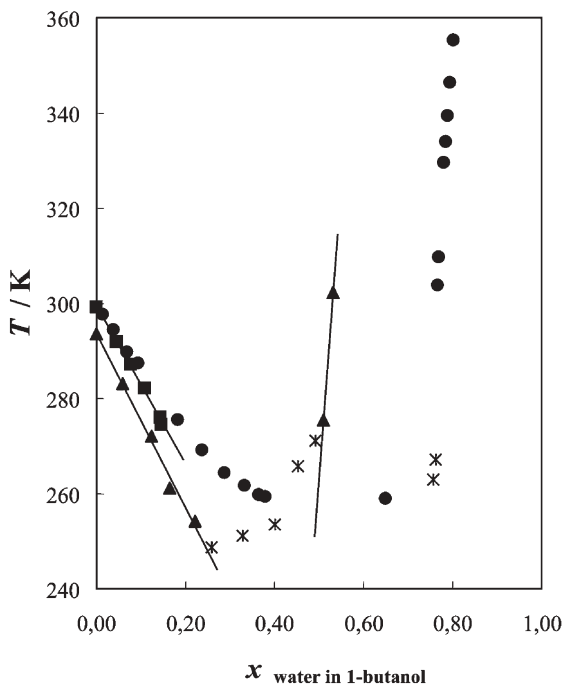

Fig. 4 Effect of addition of water on the demixing temperature of [C_4mim][NTf_2]–1-butanol mixtures: near-critical (■ initial w_{IL} = 0.4407, ● initial w_{IL} = 0.4517) and off-critical (▲ initial w_{IL} = 0.1616); * represents transitions from homogeneous liquid mixture to the solid. The lines are drawn as guides to the data.

Table 1 Cloud-point data and their pressure dependence for [C_4mim][NTf_2]–1-butanol–water. w_{IL} represents the weight fraction of [C_4mim][NTf_2] with respect to the whole solution. x_{HO} is the mole fraction of water in the water–1-butanol mixture

w_{IL}	x_{HO}	p/bar	T/K	$dT/dp \times 10^3$/K bar^{-1}
0.1312	0.5319	1	302	—
0.1333	0.5101	1	276	—
0.1527	0.2220	1	254	—
0.1554	0.1646	1	261	—
0.1571	0.1241	1	272	—
0.1596	0.0585	1	283	—
0.1616	0	1	294	—
0.2028	0	1	296	—
		2.2	297.12	
		10.7	297.09	
0.2220	0	19.9	297.06	−3.37
		30.1	297.02	
		41.4	296.99	
0.2361	0	1	297	—
0.2813	0	1	298	—
0.2937	0.8016	1	355	—
		2.9	282.32	
		12.9	282.28	
0.2960	0.0990	21.6	282.27	−3.45
		31.1	282.22	
		40.2	282.19	
0.2986	0.7938	1	346	—
0.3017	0.7888	1	340	—
0.3045	0.7840	1	334	—
0.3066	0.7805	1	330	—
0.3084	0	1	299	—
0.3128	0.7693	1	310	—
0.3144	0.7664	1	304	—
0.3336	0	1	299	—
0.3353	0.0452	1	292	—
0.3371	0.0768	1	287	—
0.3390	0.1078	1	282	—
0.3414	0.1431	1	276	—
0.3420	0.1458	1	275	—
0.3623	0.6496	1	259	—
0.3888	0	1	299	—
0.4177	0.3793	1	259	—
0.4197	0.3644	1	260	—
0.4215	0.0000	1	299	—
0.4236	0.3327	1	262	—
0.4287	0.2875	1	264	—
0.4337	0.2377	1	269	—
0.4386	0.1831	1	276	—
0.4407	0	1	299	—
0.4432	0	1	299	—
0.4456	0.0933	1	287	—
0.4473	0.0684	1	290	—
0.4494	0.0378	1	294	—
0.4509	0.0135	1	298	—
0.4517	0	1	299	—
0.4928	0	1	299	—
		2.0	299.09	
		14.8	299.03	
0.5107	0	25.7	299.00	−3.73
		41.3	298.95	
		42.6	298.95	
0.5259	0	1	299	—
0.6004	0	1	299	—
0.7607	0	1	291	—

occurs up to a point (typically 1 : 1 mole ratio of water–alcohol) where further addition of water induces an increase in the demixing temperature. For some concentrations of ternary mixtures a transition from one liquid phase to solid has been observed (stars in Fig. 4).

Although not numerous, the set of cloud-points data taken from Table 1 enables one to construct a semi-quantitative ternary phase diagram (Fig. 5) at 288 K and atmospheric pressure. All experimental data have been interpolated to the temperature of 288 K. Mutual solubilities of (1-butanol–water) at 288 K were taken from Stephenson and Stuart[31] while the solubilities of [C_4mim][NTf_2]–water were used as given by Crosthwaite *et al.*[30] While the system ([C_4mim][NTf_2]–water) is basically immiscible,[30] both ([C_4mim][NTf_2]–1-butanol) and (1-butanol–water) mixtures show partial miscibility. When all three components are mixed together the ternary system becomes more and more miscible at least up to a certain composition. As mentioned above, the same pattern of behaviour was found in several mixtures of (RTILs–alcohol–water) whereby all combinations tested so far involve RTILs based on the 1-butyl-3-methylimidazolium cation. Ionic liquids do not expand significantly upon addition of carbon dioxide,[14f] a fact that suggests the existence of free-volumes or void space. This feature may allow water and alcohol to be dissolved together in the IL whilst maintaining the bulk alcohol–water hydrogen-bonding structure.[4]

Vapour–liquid equilibrium of 1-butanol–CO_2 mixtures—testing the new high-pressure cell

In order to check the new apparatus for determining cloud points, vapour–liquid equilibrium of an already studied system 1-butanol–CO_2 has been determined for three different compositions. Table 2 reports the demixing pressures at several temperatures.

Fig. 6 represents comparisons made with literature data[25] on the same system. These literature data are interpolated with respect to composition. In view of the fact that all authors have used quite different methods for the detection of cloud points (static-analytic, flow-analytic, and high-pressure densitometer methods) there is reasonable agreement between our experimental data and those found in the literature.

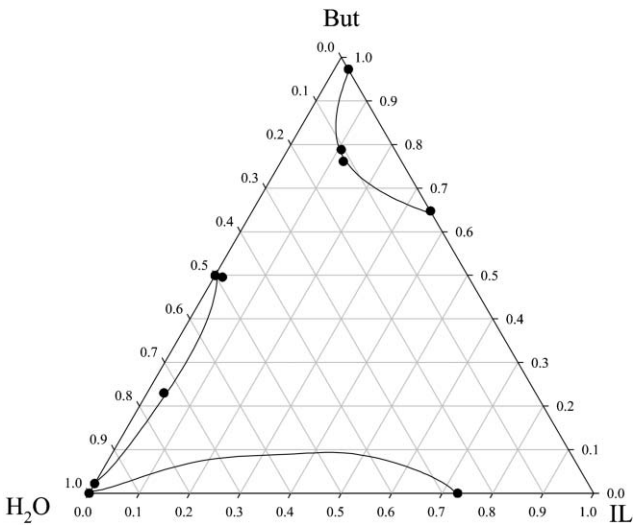

Fig. 5 Ternary phase diagram of the ([C_4mim][NTf_2]–1-butanol–water) system at 288 K and atmospheric pressure (compositions in mole fraction).

Table 2 Experimental data for the vapour–liquid equilibrium of 1-butanol–CO_2; x_{CO2} represents the mole fraction of CO_2 in the initial liquid solution

T/K	p/bar
$x_{CO_2} = 0.442$	
313.15	63.9
323.15	71.7
333.15	80.0
$x_{CO_2} = 0.598$	
298.15	57.2
313.15	75.8
323.15	96.5
333.15	102.7
$x_{CO_2} = 0.769$	
313.15	77.9
323.15	94.5
333.15	107.6

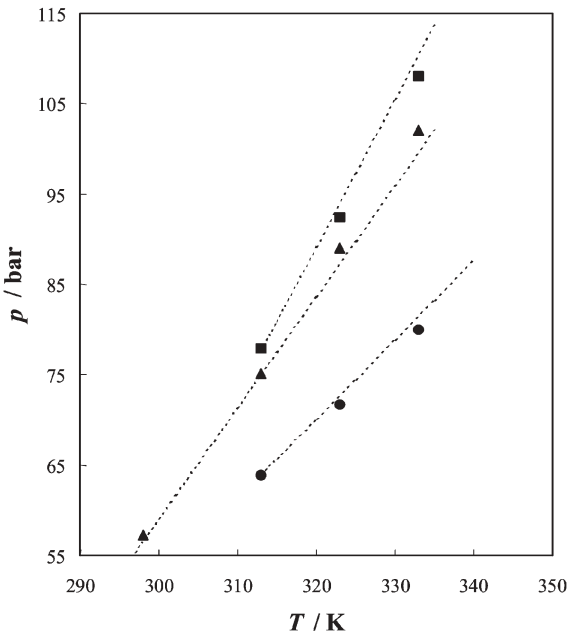

Fig. 6 Experimental p–T cloud points for the system (1-butanol–CO_2), for three different concentrations: ● $x_{CO2} = 0.442$; ▲ $x_{CO2} = 0.599$; and ■ $x_{CO2} = 0.769$. x_{CO2} is the overall mole fraction of carbon dioxide. The lines represent average values of results given in ref. 25. Above the line the system is in the one-phase region, and below it in the two-phase domain.

Vapour–liquid equilibrium of the quaternary ([C_4mim][NTf_2]–1-butanol–water–CO_2) mixture

For these VLE experiments, the new high-pressure cell described in the Experimental section was used. Phase transitions were observed either visually (through the sapphire windows) or using the light scattering method. Cloud-point data for all mixtures are presented in Table 3.

In order to compare the behaviour of mixtures with and without the ionic liquid, the study of the ternary mixture (1-butanol–water–CO_2) was included in this work. This was done to overcome the lack of vapour–liquid equilibrium data on this ternary system at about room temperature.

Only in the case of the quaternary mixture No 2 (see Table 3) it was possible to obtain a visual observation of transitions

Table 3 Cloud-point data of the quaternary ([C_4mim][NTf_2]–1-butanol–water–CO_2) and ternary (1-butanol–water–CO_2) systems; x_i represents the mole fraction

	Estimated composition			Cloud-point data	
No	x_{IL}	$x_{1\text{-butanol}}$	$x_{CO_2 calc.}$	T/K	p/bar
1	0.046	0.257	0.628	302.25	68.5
				313.15	96.5
				323.15	137.9
				333.15	158.6
2	0.025	0.295	0.587	295.6	213.7
3	0.016	0.087	0.868	296.70	218.4
				298.65	417.1
				298.75	448.2
				299.13	489.5
				299.35	517.1
				300.67	558.5
				301.10	596.4
				301.44	701.5
				301.60	723.9
				313.15	965.3
4	0.016	0.078	0.859	296.15	806.7
5	0	0.363	0.526	297.15	59.6
6	0	0.343	0.509	297.15	641.2
7	0	0.352	0.517	297.15	339.6

from the two-phase to the three-phase regions. In the other cases, the limited visual field (vacant diameters of sapphire windows are approximately 6 mm, while the length of the cell varies from 42 to 193 mm) prevented similar observations. Fig. 7 shows the development of phases as pressure changes for mixture No 2 at room temperature (295.6 K). In Fig. 7 (I) the system is in the two-phase region; the lower phase is the RTIL-rich phase and the upper one is the CO_2-rich phase. By moving the piston backwards, pressure was slowly decreased up to the moment when the first sign of turbidity was observed (Fig. 7 (II)). This cloud-point pressure was recorded. From this point on, if we allow the system to stabilize (for about 10 minutes), it will turn into a transparent three-phase system with clear menisci, as in Fig. 7 (IIa). A further decrease in pressure provoked the reappearance of turbidity (Fig. 7 (III)) and, again, waiting for several minutes resulted in three clear phases as shown in Fig. 7 (IIIa). Note that the volume of the intermediate phase has increased (Fig. 7 (IV) and (V)). For all other mixtures, cloud points were observed using the light scattering technique as described in the Experimental section.

In order to compare the behaviour of the quaternary ([C_4mim][NTf_2]–1-butanol–water–CO_2) and ternary (1-butanol–water–CO_2) systems Fig. 8 has been drawn (pressure of phase changes, p, as a function of the overall mole fraction of water with respect to butanol–water, $x_{water\ in\ 1\text{-butanol}}$). In the case of mixtures 1 and 3, an extrapolation of pressure of the phase change was performed to $T = 297.15$ K (the temperature

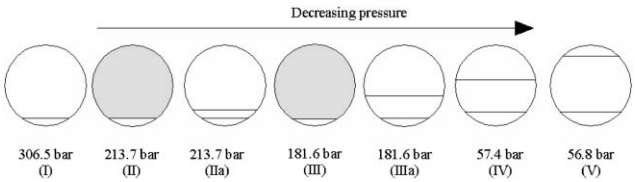

Fig. 7 Phase changes as pressure decreases at room temperature for mixture No 2 in Table 3 (see text).

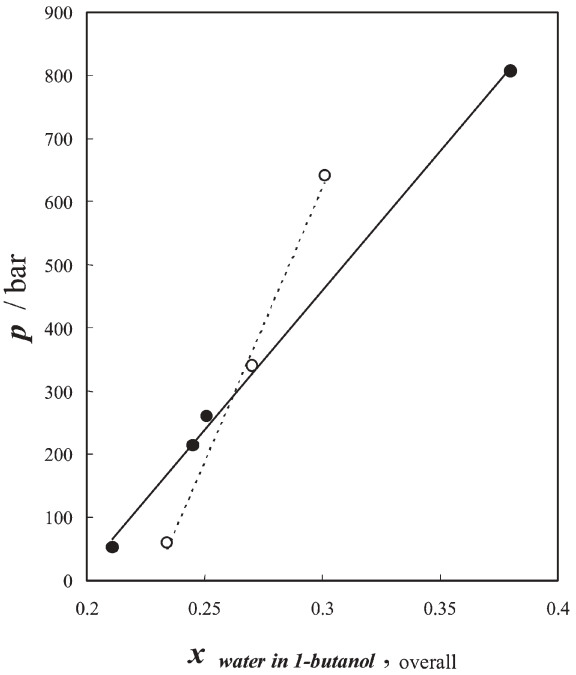

Fig. 8 Demixing pressure p of [C_4mim][NTf_2]–1-butanol–water–CO_2 (●) and 1-butanol–water–CO_2 (○) as a function of the overall mole fraction of water with respect to 1-butanol at 297.15 K. All points correspond to data reported in Table 3. The lines (full line for the quaternary mixture and dashed line for the ternary one) are drawn as guides to the data.

at which the experiments for the ternary mixture were carried out). The dashed line in Fig. 8 reflects the demixing pressure of the ternary (1-butanol–water–CO_2) system, whereby the system is in the one-phase region above the line and in the two-phase region below it. The full line in Fig. 8 represents the demixing pressure of the quaternary ([C_4mim][NTf_2]–1-butanol–water–CO_2) system, whereby above the line the system is in the two-phase region and below it in the three-phase region. An interesting observation follows from Fig. 8: the pressure of the transition is strongly dependent on the $x_{\text{water in 1-butanol}}$. Both the ternary and quaternary mixtures show similar trends—along with an increase of water fraction, the demixing pressure increases and the systems become increasingly immiscible. Note that there is a difference between the slopes for the quaternary and ternary mixtures (see Fig. 8).

It remains to be seen whether the two lines from Fig. 8 would coincide or not if the mole fraction of water with respect to butanol–water, $x_{\text{water in 1-butanol}}$ in the upper phase (CO_2-rich phase) could be used instead of overall values. In order to undoubtedly clarify and substantiate the role of the ionic liquid on the phase behaviour, another analytical method that allows for the sampling of phases must be used. Investigations to elucidate this point are currently under way in our laboratories.

Conclusion

Similar to other systems which involve RTILs and alcohols as solvents, the [C_4mim][NTf_2]–1-butanol system presents upper critical solution temperature (UCST) behaviour. For the same system, the influence of hydrostatic pressure on cloud points is rather modest. Although the [C_4mim][NTf_2]–1-butanol system shows partial mutual solubility and the [C_4mim][NTf_2]–water system is almost totally immiscible, the mutual solubility of the ternary [C_4mim][NTf_2]–1-butanol–water system is enhanced. Thus, water shows a strong co-solvent effect with alcohols.

A new apparatus that employs a high-pressure variable-volume cell, based on the synthetic method, was built, tested and used in order to determine the vapour–liquid equilibrium of ternary (1-butanol–water–CO_2) and quaternary ([C_4mim][NTf_2]–1-butanol–water–CO_2) systems. The results for both mixtures suggest that the demixing pressure is strongly controlled by the water concentration.

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Preparation of biotin derivatives by catalytic oxidative carbonylation of diamines

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Biotin methyl ester and related heterocyclic ureas were synthesized by $W(CO)_6$-catalyzed oxidative carbonylation of the corresponding diamines. This procedure provides an alternative to the use of phosgene and phosgene derivatives for formation of the urea moiety.

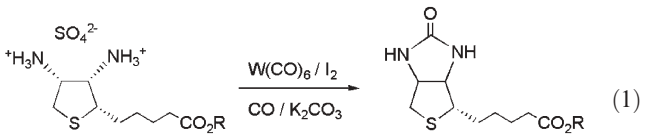
Introduction

Biotin (**1b**), also known as Vitamin H, is a cofactor for biochemical carboxylations. It is manufactured on a large scale as a feed additive for poultry and swine. In addition to its commercial value, biotin has been of great interest as a synthetic target. More than 40 total and formal syntheses have appeared since 1943, when the first racemic synthesis was reported.[1] Many of these approaches involve conversion of a diaminotetrahydrothiophene moiety into the bicyclic urea core. Two general means of achieving this transformation are used repeatedly: 1) reaction of a tetrahydrothiophene diamine with phosgene[2–4] and 2) hydrolysis of a bis(carbamate) derivative of the diamine so that generation of the first free amine triggers ring closure by nucleophilic attack on the remaining carbamate.[5,6]

The strategies for biotin preparation reflect the most common approach to the formation of ureas, nucleophilic reaction of amines with phosgene or phosgene derivatives.[7] Concerns about phosgene[8] and the value of multiple methodologies for a given chemical transformation have led us to explore catalytic methods for the conversion of amines to ureas. We previously reported the catalytic oxidative carbonylation of primary and secondary amines to ureas using $W(CO)_6$ as catalyst, I_2 as the oxidant and CO as the carbonyl source.[9–14] Tolerance of functional groups is broad and five- to eight-membered cyclic ureas are accessible from the corresponding diamines.[11,13,14] The first application of this methodology to a functionalized target was formation of the core structure of the HIV protease inhibitors DMP 323 and DMP 450.[15] We now report preparation of biotin methyl ester and related bicyclic systems by catalytic carbonylation of the corresponding diamines.

Results and discussion

Initial attempts to synthesize biotin by oxidative carbonylation of the ammonium salt **1a** under the standard conditions were unsuccessful (eqn. (1)). Varying the solvent, temperature, reaction time and the amount of catalyst did not result in the formation of biotin. Since **1a** was recovered as a solid at the end of the reaction, we concluded that the low solubility of **1a** in CH_2Cl_2 was probably responsible for the failure to obtain the urea.

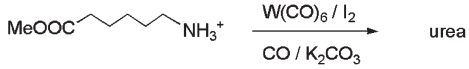


(1)

1a R = H
2a R = Me

1b R = H (0%)
2b R = Me (84%)

Based on previously reported functional group compatibility studies,[13] the carboxylic acid moiety of **1a** had been expected to present a problem in the direct synthesis of biotin. Thus, we carried out model studies using 6-aminocaproic acid as the substrate. The results were similar to those for compound **1a**. Only trace amounts of the corresponding urea were detected in ^{13}C NMR spectra of the reaction mixtures and approximately 90% of the starting material could be recovered. In contrast, when the methyl ester of 6-aminocaproic acid (**3a**) was carbonylated, 70% yield of the corresponding urea was obtained in 4 h at room temperature (eqn. (2)).



(2)

3a **3b** (70%)

To obtain a biotin precursor that was soluble in organic solvents, carboxylic acid **1a** was converted to its methyl ester **2a** using $SOCl_2$ in methanol.[16] Carbonylation of **2a** to biotin methyl ester (**2b**) at room temperature was complete in around 8 h. When the temperature was raised to 50 °C, the reaction time was decreased to 1 h and the yield of **2b** was improved to 84%. Longer reaction times resulted in decomposition of the product.

Related diamines such as the tetrahydrofuran derivatives **4a** and **5a** were also studied based on the promising results obtained from biotin methyl ester (Table 1, eqn. (3)). Unfortunately, carbonylation of **4a** afforded "chainless oxybiotin" **4b** in trace amounts. Attempts to optimize the reaction conditions by varying the amount of catalyst, or reaction time and temperature did not produce higher yields of **4b**. The low solubility of diamine **4a** in methylene chloride was clearly problematic and the solubility of urea **4b** in water prevented use of the usual workup, which involves extraction. An alternative workup using ion exchange resins did not

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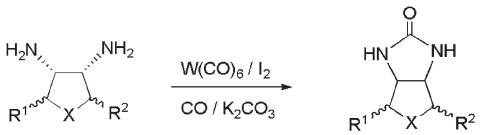
Table 1 Yields of bicyclic ureas from diamines **4a**–**5a**, **7a**–**8a**

Amine	Urea	$W(CO)_6/I_2$ yield[a]	CDI yield
4a	**4b**	Trace	20%
5a	**5b**	47%	67%
7a	**7b**	46%	37%
8a	**8b**	57%[b]	56%[c]
9a	**9b**	4%[d]	—[e]

[a] Unless otherwise noted, all reactions were carried out in CH_2Cl_2 (40 mL) at room temperature under 80 atm of CO. Diamine (1 mmol), $W(CO)_6$ (4 mol%), K_2CO_3 (3 mmol), I_2 (1 mmol). [b] Yield based on diamine consumed (47%). [c] Yield based on diamine consumed (70%). [d] Conditions as above except pyridine (1.0 mL) was used as the base and the reaction was carried out at 50 °C. [e] Reaction not attempted.

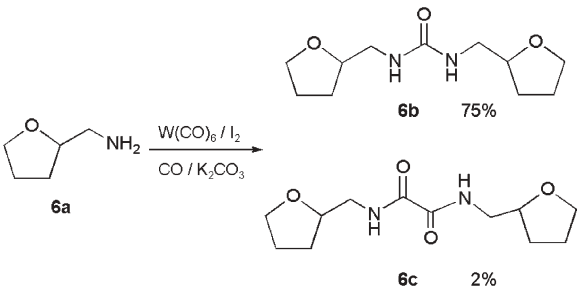
provide an improvement. Note that reaction of **4a** with the phosgene derivative 1,1′-carbonyldiimidazole (CDI) also afforded **4b** in low yield.



4a-5a,7a-8a **4b-5b,7b-8b** (3)

		X	R^1	R^2
4a	**4b**	O	H	H
5a	**5b**	O	H	$(CH_2)_4CH_3$
7a	**7b**	N-BOC	CH_3	CH_3
8a	**8b**	CH_2CH_2	H	H

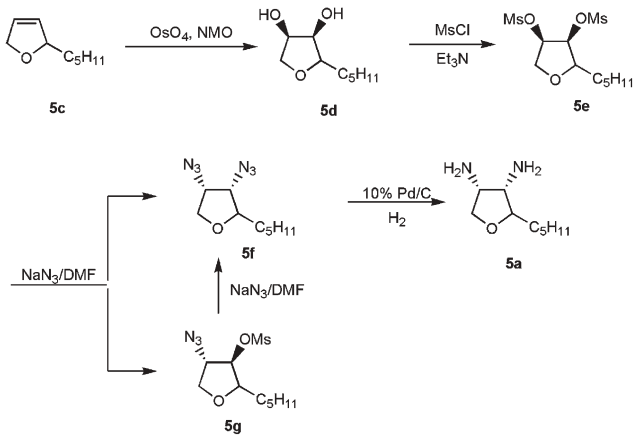
Since an alternative explanation of the low yields from **4a** involved reactivity of tetrahydrofuran rings under the reaction conditions, the model compound tetrahydrofurfurylamine (**6a**) was subjected to catalytic carbonylation to test the stability of the ring (eqn. (4)). The yields of urea **6b** were dependent upon the amount of K_2CO_3 in the reaction mixtures and reached a maximum value of 75% when 1.0 equiv. of K_2CO_3 was used. Oxamide **6c** was obtained in 2% yield as a byproduct of this reaction.



6a **6b** 75% **6c** 2% (4)

In order to test a tetrahydrofuran derivative with higher solubility in organic solvents, diamine **5a** was prepared from the corresponding diol *via* the dimesylate and diazide (Scheme 1) and subjected to the carbonylation reaction under 85 atm of CO at room temperature for 30 h. The pure urea **5b** was obtained in 47% yield as a white solid. Due to the sensitivity of diamine **5a**, attempts to recover remaining starting material from the reaction mixtures failed.

Nitrogen-containing heterocycles were investigated by carbonylation of *N-tert*-butoxycarbonyl-2,5-dimethyl-3,4-diaminopyrrolidine **7a** at room temperature for 8 h. Urea **7b** was isolated in 46% yield after chromatography on silica gel.



5c **5d** **5e** **5f** **5a** **5g**

Scheme 1 Synthetic route to **5a**.

Longer reaction times and higher temperatures caused the yield of urea to decrease due to the formation of decomposition products. In comparison, conversion of **7a** to **7b** using the stoichiometric carbonylation reagent CDI afforded the urea in only 37% yield.

The carbocyclic substrates *trans*-1,2-diaminocyclohexane (**8a**) and *cis*-1,2-diaminocyclopentane (**9a**) were also subjected to the carbonylation conditions. The conversion of **8a** to the corresponding urea **8b** proceeded in moderate yield. Note that **8a** had previously been reported to be a problem substrate for conversion to the urea with phosgene.[17] Although the yield of **8b** from catalytic carbonylation is modest, it is comparable to the yield from **8a** and CDI. Carbonylation of cyclopentane derivative **9a** was unsuccessful due to its instability and the insolubility of its diammonium salt in methylene chloride. Very low yields of **9b** were obtained after chromatography and characterization by ^1H NMR and HRMS.

In summary, catalytic oxidative carbonylation has been applied to the preparation of biotin methyl ester and related bicyclic systems as an alternative to phosgene or phosgene derivatives. Yields of the ureas are moderate to good and depend on the solubility of the diamine and urea in methylene chloride. Further applications of this methodology to the synthesis of complex targets are still under investigation.

Experimental

General

Solvents were purged with nitrogen and dried by passing the degassed solvent through a column packed with activated alumina.[18] All other chemicals were purchased in reagent grade and used with no further purification unless stated otherwise. $W(CO)_6$ was purified by chromatography on silica gel using hexane as eluent.

5-(3,4-Diammoniumtetrahydrothiophen-2-yl)pentanoic acid, sulfate salt (1a)

The hydrolysis product of biotin was prepared in 78% yield as previously described.[19] ^1H NMR (D_2O): δ 4.23 (m, 2H), 3.86 (m, 1H), 3.36 (m, 1H), 3.01 (m, 1H), 2.39 (t, 2H), 1.86 (m, 1H), 1.62–1.35 (m, 5H); ^{13}C NMR (D_2O): δ 179.8, 57.2, 54.9, 47.6,

34.5, 30.4, 28.8, 28.1, 24.8; Anal. Calcd for $C_9H_{20}N_2O_6S_2$: C 34.17, H 6.37, N 8.85; found: C 34.02, H 6.31, N 8.51.

5-(3,4-Diammoniumtetrahydrothiophen-2-yl)pentanoic acid methyl ester, sulfate salt (2a)

MeOH (2 mL) was cooled in an ice–salt bath. Thionyl chloride (0.04 mL, 0.6 mmol) was added dropwise with stirring, followed by the diaminocarboxylic acid sulfate **1a** (54 mg, 0.17 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 3 days. The clear solution was then concentrated under vacuum to afford an off-white solid in quantitative yield. The product was identified by comparison to literature data.[20]

Biotin methyl ester (2b)

The crude diamine **2a** (82.5 mg, 0.25 mmol) was dissolved in 3 mL of H_2O, neutralized to pH = 5 by adding 1 N KOH solution and diluted to a total of 5 mL. The solution was transferred to a glass-lined 300 mL Parr high pressure vessel, followed by addition of $W(CO)_6$ (4 mg, 0.01 mmol), K_2CO_3 (138 mg, 1.00 mmol), I_2 (63.5 mg, 0.250 mmol) and 15 mL of CH_2Cl_2. The carbonylation reaction was run at 50 °C for 70 min under 85 atm of CO. After the pressure was released, the aqueous solution was separated from the CH_2Cl_2 layer and extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$ and the solvent removed. The crude pale brown solid was rinsed with hexane to afford 54 mg (84% yield) of pure **2b**. The product was identified by comparison to literature data.[21]

2-Pentyl-*cis*-3,4-dihydroxytetrahydrofuran (5d)

2-Pentyl-2,5-dihydrofuran (**5c**)[22] (0.589 g, 4.20 mmol), 4-methylmorpholine *N*-oxide (2.95 g, 25.2 mmol) and OsO_4 (4 wt% aq. solution, 1.59 mL, 0.252 mmol) were added to 16 mL of 3 : 1 CH_2Cl_2 : THF and stirred at room temperature for 14 h. Then an aqueous solution of $Na_2S_2O_5$ (20 mL) was added. The mixture was stirred for 1 h and the two layers were then separated. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvent, a dark brown residue was obtained. Chromatography on silica gel (1 : 1 hexane : EtOAc) afforded the pure 2-pentyl-*cis*-3,4-dihydroxytetrahydrofuran (**5d**) as a mixture of isomers in 59% yield. ^{1}H NMR ($CDCl_3$): δ 4.21 (m, 1H), 4.10 (m, 1H), 3.78–3.62 (m, 3H), 3.54 (d, 1H), 3.41 (d, 1H), 1.67–1.30 (m, 8H), 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 82.8, 76.1, 72.7, 71.2, 33.5, 32.1, 25.7, 22.8, 14.2; Anal. Calcd for $C_9H_{18}O_3$: C 62.04, H 10.41; found: C 62.10, H 10.61.

2-Pentyl-*cis*-3,4-di-*O*-methylsulfonyltetrahydrofuran (5e)

2-Pentyl-*cis*-3,4-dihydroxytetrahydrofuran (**5d**) (0.174 g, 1.00 mmol), Et_3N (0.313 g, 3.09 mmol) and methylsulfonyl chloride (0.252 g, 2.20 mmol) were added to 10 mL of dry CH_2Cl_2 and stirred in an ice–acetone cold bath (−10 °C) for 1 h. Then the reaction mixture was diluted with CH_2Cl_2 and washed with 0.12 N HCl, saturated $NaHCO_3$, and H_2O. The solution was dried over $MgSO_4$ and the crude product was obtained by evaporation of the solvent. Flash chromatography on silica gel (2 : 1 hexane : EtOAc) afforded a white solid as a mixture of isomers in 97% yield. ^{1}H NMR ($CDCl_3$): δ 5.16 (m, 1H), 4.68 (m, 1H), 4.25 (m, 1H), 4.00 (m, 2H), 3.13 (d, 6H), 1.75–1.30 (m, 8H), 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 79.9, 78.9, 76.4, 70.6, 38.8, 32.6, 31.8, 25.2, 22.7, 14.2; Anal. Calcd for $C_{11}H_{22}O_7S_2$: C 39.98, H 6.71; found: C 40.25, H 6.74.

2-Pentyl-*cis*-3,4-diazidotetrahydrofuran (5f)

To 25 mL of dry DMF, 2-pentyl-*cis*-3,4-di-*O*-methylsulfonyltetrahydrofuran (**5e**) (0.783 g, 2.37 mmol) and NaN_3 (2.16 g, 33.2 mmol) were added and heated at 150 °C for 24 h. After the mixture was cooled to room temperature, water was added to dissolve the pale brown solid. This solution was then extracted three times with 1 : 1 Et_2O : hexane. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The pure diazide (**5f**) was obtained as a single diastereomer by chromatography on silica gel (8 : 1 hexane : EtOAc) in 46% yield as a colorless oil. Further elution with 4 : 1 hexane : EtOAc afforded the monosubstituted azide product **5g** (0.138 g, 21%). Compound **5g** was dissolved in DMF (15 mL), and NaN_3 (0.259 g, 4.0 mmol) was added to the solution. The mixture was stirred at 145 °C for 21 h. After the workup as described above and chromatography on silica gel, an additional amount of pure **5f** (0.031 g) was obtained. The total yield of **5f** was 52%. ^{1}H NMR ($CDCl_3$): δ 4.24 (m, 1H), 4.01 (m, 2H), 3.88 (m, 1H), 3.80 (m, 1H), 1.73–1.30 (m, 8H), 0.90 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 81.5, 68.7, 65.6, 63.2, 38.8, 31.9, 30.2, 25.9, 22.7, 14.2; Anal. Calcd for $C_9H_{16}N_6O$: C 48.20, H 7.19, N 37.47; found: C 48.40, H 7.39, N 37.73.

2-Pentyl-*cis*-3,4-diaminotetrahydrofuran (5a)

2-Pentyl-*cis*-3,4-diazidotetrahydrofuran (**5f**) (0.244 g, 1.09 mmol) and 40 mg of 10% Pd/C were added to 6 mL of MeOH. The reaction mixture was degassed and refilled with H_2 at 1 atm and then stirred at room temperature for 18 h until no starting material was evident by TLC. The mixture was filtered through Celite and solvent was removed to yield the crude product. Pure **5a** was obtained as a single diastereomer by chromatography on silica gel (10% MeOH in CH_2Cl_2 with 1% Et_3N) as a colorless oil in 82% yield. ^{1}H NMR ($CDCl_3$): δ 3.97 (t, 1H), 3.84 (m, 1H), 3.61 (m, 1H), 3.40 (t, 1H), 3.11 (m, 1H), 1.59–1.31 (m, 8H), 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 82.4, 72.2, 55.9, 55.3, 32.2, 30.2, 26.1, 22.8, 14.2; Anal. Calcd for $C_9H_{20}N_2O$: C 62.75, H 11.70, N 16.26; found: C 62.39, H 12.05, N 15.59.

4-Pentyltetrahydrofuro[3,4-*d*]imidazol-2-one (5b)

To a glass lined 300 mL Parr high pressure vessel were added 2-pentyl-*cis*-3,4-diaminotetrahydrofuran (**5a**) (220 mg, 1.28 mmol), $W(CO)_6$ (18 mg, 0.051 mmol), K_2CO_3 (530 mg, 3.84 mmol), I_2 (325 mg, 1.28 mmol) and 45 mL of CH_2Cl_2. The reaction was run under 85 atm of CO at room temperature for 30 h. After the pressure was released, the solid was collected by filtration and washed with chloroform. The combined organic solutions were evaporated to dryness to afford a brown solid.

The pure product (118 mg) was obtained as a single diastereomer by chromatography on silica gel (20 : 1 EtOAc : MeOH) as a white solid in 47% yield. mp: 105–107 °C; IR (CH_2Cl_2): ν_{CO} 1716 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.55 (s, br, 1H), 5.33 (s, br, 1H), 4.37 (m, 1H), 4.20 (m, 1H), 3.90 (m, 2H), 3.54 (m, 1H), 3.45 (m, 1H), 1.72–1.30 (m, 8H), 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 163.3, 83.1, 74.6, 59.3, 57.9, 32.0, 29.0, 26.2, 22.8, 14.2; Anal. Calcd for $C_{10}H_{18}N_2O_2$: C 60.58, H 9.15, N 14.13; found: C 60.85, H 9.30, N 13.74.

4-Pentyltetrahydrofuro[3,4-*d*]imidazol-2-one (5b) by reaction with CDI

2-Pentyl-*cis*-3,4-diaminotetrahydrofuran (**5a**) (0.183 g, 1.06 mmol) and 0.170 g (1.05 mmol) of 1,1′-carbonyldiimidazole (CDI) were added to 40 mL of dry THF and stirred at room temperature for 21 h. After the solvent was evaporated, the white residue was dissolved in $CHCl_3$ and washed with 0.12 N HCl, followed by brine. The solution was then dried over $MgSO_4$. The crude product was purified by chromatography on silica gel (20 : 1 EtOAc : MeOH). The pure urea was obtained in 67% yield as a white solid and identified by comparison to an authentic sample prepared as above.

N-tert-Butoxycarbonyl-2,5-dimethylpyrroline (7d)

To 5 mL MeOH were added 2,5-dimethylpyrroline (0.118 mL, 0.996 mmol), di-*tert*-butyl dicarbonate (0.24 g, 1.1 mmol) and $NaHCO_3$ (250 mg). This mixture was subjected to ultrasonic irradiation for 4 h.[23] Excess $NaHCO_3$ was removed by filtration and the MeOH was evaporated under vacuum. The residue was redissolved in Et_2O and a second filtration was carried out. Evaporation of Et_2O afforded the pure product in 96% yield. The crude product was used for the next step without further purification. ^1H NMR ($CDCl_3$): δ 5.59 (m, 2H), 4.58–4.48 (m, 2H), 1.48 (s, 9H), 1.33 (d, 3H), 1.27 (d, 3H); ^{13}C NMR ($CDCl_3$): δ 153.9, 130.6, 130.3, 79.2, 60.3, 60.0, 28.8, 21.1, 19.7.

N-tert-Butoxycarbonyl-2,5-dimethyl-3,4-dihydroxypyrrolidine (7e)

The oxidation product of *N-tert*-butoxycarbonyl-2,5-dimethylpyrroline (**7d**) was prepared as described in the literature.[24] The pure product was obtained by chromatography (1 : 1 hexane : EtOAc) in 86% yield as a colorless oil. ^1H NMR ($CDCl_3$): δ 4.32 (m, 1H), 3.90 (m, 3H), 3.05 (m, 3H), 1.47 (s, 9H), 1.29 (m, 3H), 1.17 (d, 3H); ^{13}C NMR ($CDCl_3$): δ 154.6, 79.8, 70.9, 59.0, 55.3, 28.7, 18.5, 14.5; Anal. Calcd for $C_{11}H_{21}NO_4$: C 57.12, H 9.15, N 6.06; found: C 57.45, H 9.40, N 6.01.

N-tert-Butoxycarbonyl-2,5-dimethyl-3,4-di-*O*-methylsulfonylpyrrolidine (7f)

To a solution of *N-tert*-butoxycarbonyl-2,5-dimethyl-3,4-dihydroxypyrrolidine (**7e**) (0.466 g, 2.02 mmol) in 10 mL anhydrous pyridine cooled in an ice–salt bath, was added dropwise methylsulfonyl chloride (0.694 g, 6.06 mmol). After addition, the solution was slowly warmed to room temperature and allowed to stir for 4 h. After the solvent was removed, the brown residue was dissolved in CH_2Cl_2–H_2O and extracted with CH_2Cl_2. The combined organic solutions were then washed with 0.1 N HCl until the pH of the aqueous layer was acidic. After the organic solution was washed by brine and dried over $MgSO_4$, the solvent was removed under vacuum to afford **7f** as a yellow oil in quantitative yield. The compound was not purified before the next step. ^1H NMR ($CDCl_3$): δ 5.15 (m, 1H), 4.91 (m, 1H), 4.19 (m, 2H), 3.14 (m, 3H), 1.48 (s, 9H), 1.33 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 154.6, 79.8, 70.9, 59.0, 55.3, 28.7, 18.5, 14.5.

N-tert-Butoxycarbonyl-2,5-dimethyl-3,4-diazidopyrrolidine (7g)

To 20 mL of dry DMF were added *N-tert*-butoxycarbonyl-2,5-dimethyl-3,4-di-*O*-methylsulfonylpyrrolidine (**7f**) (1.161 g, 3.0 mmol) and NaN_3 (2.73 g, 42.0 mmol). The mixture was heated to 120 °C for 21 h. After cooling to room temperature, deionized H_2O and mixed solvent (3 : 2 Et_2O : hexane) were added and the layers were separated. The organic phase was dried over $MgSO_4$ and concentrated under vacuum to afford the crude product. The pure compound was obtained in 31% yield by chromatography on silica gel (5 : 1 hexane : EtOAc). ^1H NMR ($CDCl_3$): δ 4.29 (m, 1H), 4.08 (m, 1H), 3.87 (m, 2H), 1.47 (s, 9H), 1.35–1.27 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 153.5, 80.3, 67.8, 62.8, 57.6, 54.9, 28.6, 19.6, 15.6; Anal. Calcd for $C_{11}H_{19}N_7O_2$: C 46.96, H 6.81, N 34.85; found: C 47.37, H 6.94, N 34.84.

N-tert-Butoxycarbonyl-2,5-dimethyl-3,4-diaminopyrrolidine (7a)

To a 7 mL MeOH solution of *N-tert*-butoxycarbonyl-2,5-dimethyl-3,4-diazidopyrrolidine (**7g**) (0.355 g, 1.26 mmol) was added 200 mg of 10% Pd/C. The slurry was degassed and refilled three times with H_2 at 1 atm. The reaction mixture was stirred at room temperature until no starting material was evident by TLC. The catalyst was filtered through Celite and the solvent was removed to afford a pale yellow oil. Further purification by chromatography on silica gel (5% MeOH in CH_2Cl_2 with 1% TEA) afforded pure diamine **7a** in 76% yield. IR (Nujol): 3373, 3318, 1694 cm^{-1}; ^1H NMR (DMSO-d_6, 90 °C): δ 3.71 (dq, J = 8 Hz, J = 7 Hz, 1H), 3.55 (dq, J = 2 Hz, J = 7 Hz, 1H), 3.42 (dd, J = 8 Hz, J = 5 Hz, 1H), 2.95 (dd, J = 5 Hz, J = 2 Hz, 1H), 2.85 (s, br, 2H), 1.41 (s, 9H), 1.22 (d, J = 6 Hz, 3H), 1.14 (d, J = 6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 90 °C): δ 153.0, 77.6, 59.2 (2 × C), 54.7, 52.6, 27.8, 18.4, 14.5; HRMS (LSIMS): Calcd for $C_{11}H_{24}N_3O_2$ $(M+H)^+$ 230.1868, found 230.1880.

4,6-Dimethyl-2-oxo-hexahydropyrrolo[3,4-*d*]imidazole-5-carboxylic acid *tert*-butyl ester (7b)

To a 300 mL glass lined Parr high pressure vessel were added $W(CO)_6$ (16 mg, 0.045 mmol), 40 mL of CH_2Cl_2, *N-tert*-butoxycarbonyl-2,5-dimethyl-3,4-diaminopyrrolidine (**7a**) (0.26 g, 1.1 mmol), K_2CO_3 (0.47 g, 3.4 mmol), and I_2 (0.288 g, 1.13 mmol). The vessel was then charged with 85 atm of CO and left to stir at room temperature for 8 h. The pressure was released and the pale yellow solution was filtered. The CH_2Cl_2 solution was washed with 0.1 N HCl and aqueous

$Na_2S_2O_3$ solution. After drying over $MgSO_4$ and filtration, the resulting solution was then concentrated to afford a pale brown solid. The white solid urea was obtained in 46% yield after chromatography on silica gel (15 : 1 EtOAc : MeOH). mp: 232–234 °C; IR (CH_2Cl_2): ν_{CO} 1720, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.42 (s, br, 1H), 5.23 (s, br, 1H), 4.28 (m, 1H), 3.86–4.00 (m, 3H), 1.47 (s, 9H), 1.35 (d, 3H), 1.19 (d, 3H); ^{13}C NMR ($CDCl_3$): δ 163.2, 154.8, 80.1, 62.8, 56.1, 28.7, 18.5, 15.9; Anal. Calcd for $C_{12}H_{21}N_3O_3$: C 56.45, H 8.29, N 16.46; found: C 56.40, H 8.56, N 16.34.

Octahydrobenzoimidazol-2-one (8b)

To a glass lined 300 mL Parr high pressure vessel were added $W(CO)_6$ (28 mg, 0.08 mmol), 80 mL of CH_2Cl_2, *trans*-cyclohexane-1,2-diamine (**8a**) (0.23 g, 2.0 mmol), K_2CO_3 (0.828 g, 5.99 mmol), and I_2 (0.508 g, 2.00 mmol). The vessel was then charged with 75 atm of CO and left to stir at 120 °C for 52 h. The pressure was released after cooling to room temperature and the brown solution was filtered. The CH_2Cl_2 solution was washed with 0.1 N HCl, dried over $MgSO_4$ and filtered. The resulting solution was then concentrated to afford a pale brown solid. The white solid urea was obtained after chromatography on silica gel (EtOAc) in 58% yield based on conversion. Unreacted starting material was recovered as the diammonium salt in 53% yield. The urea was identified by comparison to literature data.[17]

Hexahydrocyclopentaimidazol-2-one (9b)

To a glass lined 300 mL Parr high pressure vessel were added $W(CO)_6$ (28 mg, 0.08 mmol), 80 mL of CH_2Cl_2, *cis*-cyclopentane-1,2-diammonium chloride (the hydrochloride salt of **9a**) (0.454 g of the trihydrate, 2.00 mmol), pyridine (1.0 mL), and I_2 (0.508 g, 2.00 mmol). The vessel was then charged with 87 atm of CO and left to stir at 50 °C for 14 h. The pressure was released after cooling to room temperature and the brown solution was filtered. The CH_2Cl_2 solution was washed with aqueous $Na_2S_2O_3$ solution and the solvent was removed to afford a pale brown solid. The white solid urea was obtained after chromatography on silica gel (5% MeOH in EtOAc) in 4% yield. ^1H NMR ($CDCl_3$): δ 1.70 (m, 6H), 4.24 (m, 2H), 4.67 (s, 2H). HRMS (EI): Calcd for $C_6H_{10}N_2O$ (M^+) 126.0793, found 126.0792.

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The automation of continuous reactions in supercritical CO_2: the acid-catalysed etherification of short chain alcohols

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We describe a new, automated apparatus for continuous catalytic reactions in supercritical carbon dioxide, $scCO_2$. The reactor incorporates on-line sampling, enabling us to quantify gaseous products such as light alkenes, which would normally be lost in the decompression stage of more conventional supercritical reactors. The on-line sampling is coupled to a gas chromatograph running an isothermal program, which provides automated analysis of the reaction products. We illustrate the operation of the reactor by studying the acid-catalysed etherification of linear alcohols, C_1 to C_5, both individually and in pairs, over a range of temperatures and pressures equating to a total of 180 different experiments.

Introduction

Supercritical fluids, SCFs, are playing an increasingly important role in the development of greener chemical processes.[1,2] Recent research has largely focussed on supercritical carbon dioxide, $scCO_2$, because of its environmental acceptability and relatively low critical temperature, 31.1 °C. Much of the work has involved heterogeneously catalysed reactions in $scCO_2$[3–5] because these reactions lend themselves to continuous reactors and, in most cases, are inherently simpler to scale-up than processes involving homogeneous catalysis. In this context, SCFs offer the potential advantages of improved mass transport, facile separation of product from solvent, greater selectivity and increased catalyst lifetimes. Examples include hydrogenation,[6–14] oxidation,[15–21] hydroformylation[22–26] and a range of acid-catalysed reactions.[27–33]

Our own work[4,5] in $scCO_2$ has mostly involved hydrogenation[12–14] and acid-catalysed reactions.[31–33] Recently, in collaboration with Thomas Swan & Co. Ltd., we have been able to scale some of these reactions up to a full-size commercial plant. Interestingly the optimised reaction conditions for the first two reactions, the hydrogenation of isophorone[34] and acid-catalysed dehydration of butan-1,2-diol,[35] have been virtually identical on the 1000 tons *p.a.* plant and in a 5 mL reactor. This observation enormously increases the relevance and value of laboratory-scale reactions in the development and optimisation of new processes.

The continuous acid-catalysed dehydration of alcohols in $scCO_2$ to form the corresponding ethers was first described five years ago.[32] Since then, there has been almost no work in this field. The reaction proceeds with high conversion for a number of *n*-alcohols and offers a cleaner approach to ether formation than the more conventional routes with mineral acids or the Williamson synthesis.[36] Although the study[32] was quite detailed, there were a number of aspects which could not be tackled because of technical limitations of the equipment. For example, little information could be obtained about the etherification of MeOH because Me_2O is too volatile to be recovered at the end of the reactor. This was an unfortunate limitation in the context of Green Chemistry because etherification with MeOH could become attractive as a "green" procedure for protection of alcohols. However, the process would be considerably less green if it also generated significant quantities of Me_2O as a by-product. In a similar way, it was not possible in the original paper[32] to quantify the generation of propene in the etherification of *n*- and *i*-propanol.

However, even in the laboratory, optimising supercritical fluid experiments remains an extremely time-consuming and often tedious activity, not least because the high compressibility of $scCO_2$ adds a whole extra dimension to the parameter space to be optimised. Furthermore, even a rough optimisation requires many control and repeat experiments to acquire a statistically useful amount of data. Therefore, we have developed a continuous SCF reactor, which can operate for days on end and is interfaced directly to a gas chromatograph, GLC, to collect analytical data completely under computer control. Parameters which can be varied automatically include the flow rates of CO_2 and substrate(s), temperature of the catalyst bed, operating pressure and conditions for the GLC analysis. Also high pressure sampling allows collection of all products, including those volatile compounds that would evaporate during the expansion stage of a non-automated reactor.

In this paper, we demonstrate the performance of our automated SCF reactor by reporting the etherification of all *n*-alcohols from C_1 to C_5 and the co-etherification of all possible pairs of alcohols, a total of 180 different reactions. These co-etherifications are important because they provide the first information about the relative reactivity of the different alcohols *via* the yields of the three possible products, R_2O, ROR′ and R'_2O. We also investigate the possibility of acid-catalysed trans-etherification reactions. We begin by describing the key features of the reactor.

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Experimental

Reactor development

One of the goals of this study was to design and test a new reactor that would yield much more data on a reaction in a much shorter time, than the current technology. In designing the reactor, three key points needed to be addressed:

1) *Minimising the time the reactor takes to reach a steady state.* Previous SCF continuous flow equipments took >1 hour to reach a steady state, thereby limiting the number of experiments that could be performed in a given time.

2) *Automating the collection and analysis of samples.* The process of sample collection in $scCO_2$ flow reactors can be a laborious and time consuming process. Volatile products are often lost during the expansion of the $scCO_2$ because the process occurs at elevated temperatures, to prevent freezing of the expansion system.

3) *Automating control of reaction parameters.* Most current $scCO_2$ reactor systems require frequent monitoring and adjustment to maintain constant reaction conditions.

To address these problems we developed a strategy shown schematically in Fig. 1. The main features are:

a) The reactor volume was decreased by a factor of at least two-fold and in some experiments up to twenty-fold, to decrease the time the reactor takes to reach a steady state. Decreasing the reactor size decreases the residence time, the thermal mass of the reactor and the hold-up of material in the whole system. Although a reduction in residence time can adversely affect conversion in a particular reaction, this can be a very positive feature for exploring the kinetics of reactions.

b) A high pressure, 4-port HPLC sample loop (Valco VICI microvolume (0.06 μL) sample loop, electronically actuated, 250 ms switching time) was connected upstream of the expansion system at the end of the reactor to remove the need for manual collection and analysis of samples. This sample loop injects an aliquot of the reaction mixture at ambient temperatures directly into a GLC (Shimadzu GC17-a v3), while the sample is still at system pressure. The total expanded volume of the injection of course depends on the system pressure; although the very small volumes injected are calculated to be less than V_{inj} thus avoiding overloading of the analytical column. This sampling and analysis regime can be computer controlled, *via* an external events relay trigger incorporated in the GLC, requiring little or no user input during the experiment. Sampling at system pressure also allows for facile collection and analysis of all gaseous and volatile products. When sampling the $scCO_2$ stream directly, the time required to observe a response in the product distribution through changes in reaction conditions is also decreased. The reason for this is two-fold: (i) by adding a sample loop the dead volume between sampling and the catalyst bed is very much reduced and (ii) collection of a representative sample of material from our previous apparatus required 15 minutes per sample.[37] Therefore collection of a 'pure' sample after changing reaction conditions would take a minimum of 30 minutes whereas collection of a sample through a sample loop should, in theory, show changes in reaction conditions almost instantaneously.

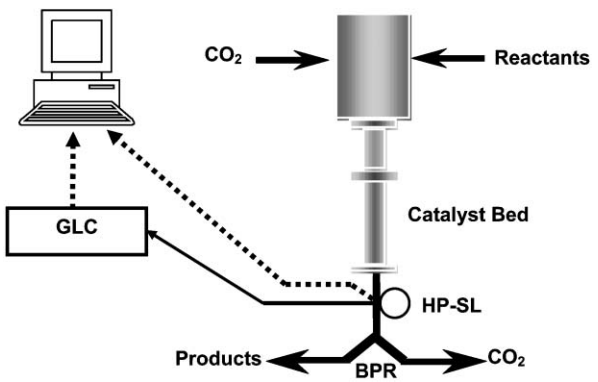


Fig. 1 The conceptual design for the automated apparatus. The design indicates automated CO_2 and reagent HPLC pumps, an automated temperature control unit and back pressure regulator, BPR. A key feature is the high pressure sample loop (HP-SL) connected to a GLC, both of which can be controlled directly through a computer. A reduced volume reaction bed decreases the time the reactor takes to reach a steady state. In this system, small aliquots of product can be analysed automatically from the outflow of the reactor bed, whilst all the reaction variables are changed automatically and independently throughout the experiment.

c) The flow control was changed to increase the operational stability and reliability of the apparatus whilst decreasing the amount of manual control and monitoring required during an experiment. A Jasco PU-1580-CO_2 chilled HPLC pump now controls the flow of the CO_2 and a Jasco BP-1580-81 back pressure regulator controls the pressure. This is the reverse of the control sequence used in our earlier equipment. Both these devices are controlled by on-board processors so that no external control is required once initial parameters are selected. With the addition of a programmable controller (CRL 455 plus) for the reaction bed temperature, all reaction conditions could be altered independently and automatically over an extended time frame. This means that by programming each device as a function of time and synchronising the start of all the programs, the product can be collected and analysed and changes in product distributions can be correlated to changes in reaction conditions.

d) The final feature of the apparatus is injection of the sample into an isothermal GLC oven. This eliminates the cooling and equilibration time between GLC programs, allowing more data to be obtained in a given period of time. It should be noted that the carrier gas flow and oven temperature must be carefully chosen to obtain good chromatographic separation whilst reducing tailing and fronting of peaks.

The high pressures and temperatures involved in reactions using $scCO_2$ mean that there are inherent hazards associated with the reactions. Therefore from the outset, several safety features were incorporated into the design of the apparatus. Both pumps contain in-built pressure monitors and trips, which cut the flow if the pressure deviates outside preset limits. An additional pressure transducer is placed upstream of the reactor and is connected to a trip that controls electrical power to all pumps and the heater. The heating controller has an independent temperature monitor that cuts the current to the heating cartridges if a preset maximum temperature is

exceeded. Apart from the gas cylinders for the GLC and the CO_2 supply, the entire apparatus is situated within a standard sized fume hood, to vent any unforeseen leakages of material. The BPR is permanently powered to avoid unintentional venting of the CO_2 gas cylinder.

To determine the time needed for the automated reactor to come to steady state, a test was carried out with a previously well characterised hydrogenation reaction, Fig. 2. This reaction was chosen because it yields three products, the distribution of which change radically with a change in reactor temperature. It can clearly be seen from the figure that the reaction reaches a steady state within 10 minutes of changing the reaction conditions. This represents an improvement of six-fold over our previous apparatus.[37]

Reaction procedures

Fig. 3 details the experimental apparatus. A CO_2 pump, JC, was connected *via* a tee-piece to a HPLC pump, J, used to deliver organic substrate, S. Both HPLC pumps could be programmed either by using the in-built menu system or by connection to a PC; in our case, the pumps were programmed manually at the user interface. CO_2 and S were pumped through an 1/8th inch tubing mixer, PH, approximately 2 m long, which was heated to reaction temperature by means of cartridge heaters and an aluminium heating block. The preheated solution was passed over the catalyst bed, R (Nafion SAC-13 or Purolite CT-175), which was heated *via* similar cartridge heaters and blocks. The temperature of the catalyst heaters could be controlled over time *via* a programmable heating controller. The mixture of products and gases passed through a HPLC 4-port sample loop, SL. The loop injects the sample into the carrier gas flow of a GLC, where product separation and analysis was carried out. The system pressure was maintained by a Back Pressure Regulator, BPR, which again could be programmed to maintain different pressure profiles at a given time. Products were collected in the waste bottle, W. The temperature was logged at several points throughout the system on a computer, PC, *via* a data recorder,

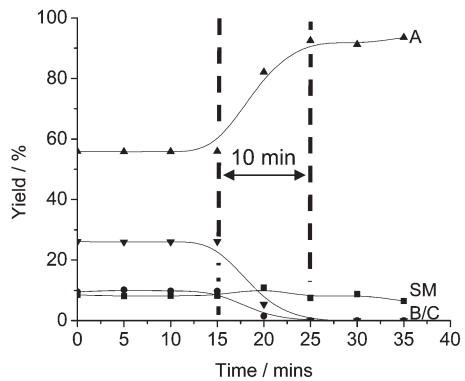


Fig. 2 A plot demonstrating the time that the reactor requires to reach a steady state. The reaction was a hydrogenation involving 4 components, starting material (SM) and three products (A, B and C). The reaction conditions were changed after 15 minutes, indicated by the dashed line. As can be seen, the product distribution reaches a steady state within 10 minutes of the change, by which time only A and the starting material can be detected.

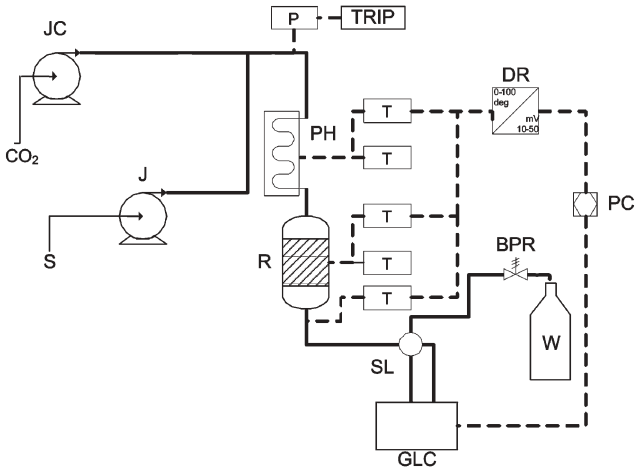


Fig. 3 Diagram for the automated apparatus. CO_2 pump, JC; HPLC pump, J; organic substrate, S;1/8th inch tubing mixer, PH; catalyst bed, R; HPLC 4-port sample loop, SL; Back Pressure Regulator, BPR; waste bottle, W; data recorder, DR; Gas-Liquid Chromatograph, GLC.

DR. Materials used: methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, pentan-1-ol, di-isopropyl ether and diethyl ether (>97%, Aldrich), Nafion SAC-13 (Dupont), Purolite CT-175 (Purolite), Amberlyst 15 (Aldrich) and CO_2 (food grade, Air Products) were used as received. All mixtures of *n*-alcohols or ethers were prepared in a 1 : 1 molar ratio and pumped through a single HPLC pump (Jasco PU980).

In a typical experiment, the catalyst was loaded into the reactor and sealed into the apparatus. After the equipment had stabilised at the required pressure and flow rate of CO_2, the reactor was heated to reaction temperature and the substrate was pumped into the system. Experimental parameters were programmed into the pumps, back pressure regulator and GLC such that all the experimental conditions could then be varied automatically by the control computer. After each experiment, the GLC batch-file was converted to a single table of peaks in ASCII format. The data was then analysed using MS Excel.

Unless otherwise stated, the standard reaction conditions were: flow of CO_2 1 mL min^{-1} at −10 °C and 58 bar, flow of the substrate 0.25 mL min^{-1} and the reactor volume 5 mL. GLC parameters: DB-5 (RTX-5, 30 m, ID 0.32 mm, film thickness, 0.25 μm) held isothermal at 40 °C for 5 minutes (column flow, 1.34 mL min^{-1}, linear velocity, 30.1 cm s^{-1}, pressure 100 kPa, split ratio, 73 : 1, injector temperature, 350 °C, FID detector temperature 300 °C). Quantification was performed by integration of the peak areas; response factors and conversions were calculated by the internal normalisation method.

Results and discussion

Our study of etherification reactions has been divided into 4 parts: (i) a study of Me_2O formation from MeOH, firstly to establish the extent of the reaction and secondly to determine how effective the new reactor is for kinetic measurements; (ii) a survey of the C_2–C_5 alcohols to measure the selectivity between

etherification and alkene formation; (iii) reactions of pairs of alcohols to compare the yields of symmetrical R_2O and R'_2O ethers with that of the unsymmetrical ether ROR′ and (iv) a study to determine whether the apparent trans-etherification reaction observed under these conditions was a genuine reaction or merely the result of sequential hydrolysis and re-etherification.

i) Formation of Me_2O

It has previously been reported[38–42] that the acid-catalysed reaction of MeOH results in the formation of Me_2O. Me_2O has a boiling point of −24.8 °C (248 K) and therefore is challenging to trap during a continuous flow synthesis. However, our use of high pressure in-line GLC injection directly at the outflow of our $scCO_2$ reactor removes this problem. The sulfonated resin Purolite CT-175 was heated to 150 °C, while a mixture of MeOH and CO_2 was passed over it. Fig. 4 summarises the effect of flow rate on the formation of Me_2O. It can clearly be seen that significant conversion occurs with up to 20% Me_2O being formed. The inverse relationship between flow rate and conversion indicates a zero order reaction under these conditions. Gogate *et al.*[43] showed that the batch etherification of MeOH, in white mineral oil as a solvent, has a reaction order of 0.28; the difference can be explained by the increased ease of mass transport in $scCO_2$.

The choice of catalyst appears to affect the conversion to Me_2O, as can be seen from Table 1, where the reaction was carried out using the stronger acid-catalyst Nafion SAC-13. Surprisingly, the conversions with Nafion SAC-13 were somewhat *lower* than with Purolite CT-175. However, the packing of Nafion SAC-13 in our reactor was significantly looser with consequently increased void space and reduced catalyst contact time. Also, the reaction using Nafion SAC-13 has a different optimal temperature and higher temperatures are needed to achieve equivalent yields. By contrast, it can be seen from Table 1 (C_1 + C_1) that at 220 °C, pressure has remarkably little effect on the overall conversion of MeOH. The detection of Me_2O in our flow reactors has a significant implication for the environmental acceptability of reactions which involve the use of MeOH as a co-solvent during acid-catalysis.

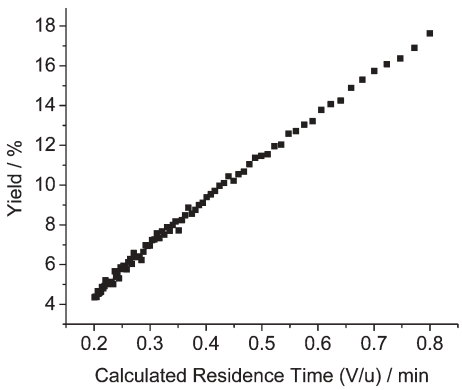


Fig. 4 Yield of Me_2O from MeOH showing the zero order of the reaction, over Purolite CT-175 catalyst at 150 °C and 100 bar. The total concentration of MeOH dissolved in $scCO_2$ was kept constant at 20% w/w. Residence time was calculated as V/u (V = reactor volume, u = fluid velocity) assuming that a single phase was present. This plot includes 85 different reaction conditions. Collecting this volume of data would require approximately 30 working days using manual reactors[13,37] but it was completed using the automated apparatus in only 14 hours.

Table 1 Percentage yield for symmetrical ethers formed from *n*-ROH alcohols over Nafion SAC-13 at different temperatures and pressures

Temperature/ °C	Pressure/ bar	Me_2O (%)	Et_2O (%)	$(n\text{-Pr})_2O$ (%)	$(n\text{-Bu})_2O$ (%)	$(n\text{-Pnt})_2O$ (%)
180	150	1.5	2.6	2.6	2.4	0.0
180	200	1.2	2.0	2.7	2.3	0.0
180	250	1.3	2.6	3.0	2.5	0.0
200	150	3.4	6.9	9.4	8.4	5.1
200	200	3.5	6.8	10.6	9.7	4.7
200	250	3.7	7.7	9.8	10.3	5.0
220	100	10.6	25.5	26.0	26.4	17.9
220	150	8.7	21.1	26.0	23.6	—
220	200	9.2	21.9	25.9	22.7	18.3
220	250	9.5	21.1	28.3	24.6	—
220	300	10.1	22.7	25.8	21.8	17.2
220	350	10.4	24.9	25.7	20.7	17.5

ii) Etherification of higher alcohols

A similar study was performed with EtOH to produce Et_2O. The results are compared to Me_2O in Fig. 5. It can be seen that the trends in conversion are similar to those observed for Me_2O, but with a near doubling of the overall conversion. Again, significant quantities of the Et_2O are formed, indicating that this reaction should be borne in mind when considering the use of EtOH as a co-solvent for $scCO_2$.

Further studies were undertaken with longer chained linear alcohols, propan-1-ol (*n*-PrOH), butan-1-ol (*n*-BuOH) and pentan-1-ol (*n*-PntOH). Table 1 shows that, as with Me_2O and Et_2O, temperature has a greater effect on yield than pressure; 220 °C, the highest temperature studied, gave the highest yields.

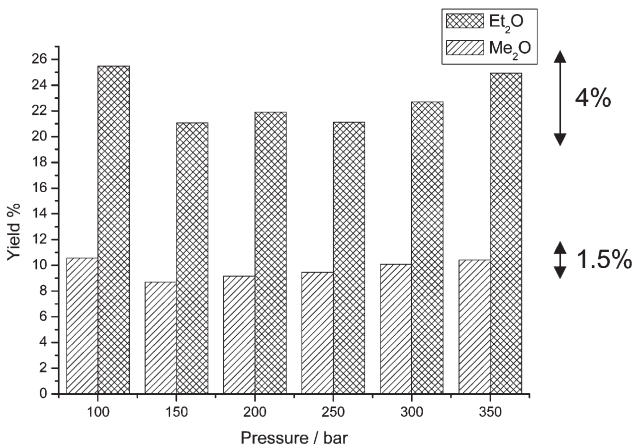


Fig. 5 Bar chart showing the small effect of pressure on the yields of Me_2O and Et_2O from the corresponding alcohols over Nafion SAC-13 acid-catalyst at 220 °C. The yield of Et_2O is more than double that of Me_2O over the same pressure range.

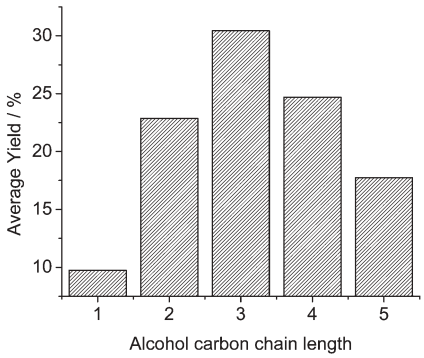


Fig. 6 The average yield of linear ethers at 220 °C from linear alcohols of different carbon chain length. The initial increase in yield can be attributed to the increased reactivity of the alcohol due to the lengthening of the carbon chain. The subsequent decrease in yield for C > 3 is due to the competing dehydration reaction to alkene formation.

As can be seen from Fig. 6, the conversion reaches a maximum for the etherification of *n*-PrOH, and falls thereafter with increasing carbon chain length. This reactivity series could be rationalised as follows. On changing from MeOH to *n*-PrOH, the alcohol becomes more nucleophilic and is therefore more reactive. This also means that, increasing the carbon chain length renders the alcohol susceptible to nucleophilic attack because protonation of the alcohol functionality can occur more readily. Hence, on increasing the carbon chain length from C_1 to C_3, the yield of the linear ether increases. The decrease in linear ether conversion for C ⩾ 3 is probably due to increased competition from the dehydration of the alcohol.

Catalyst bed temperatures have the largest effect on ether yield; nearly a ten-fold increase in yield is observed on a 40 °C increase in temperature from 180 to 220 °C. However, all alcohols experience similarly large effects on conversion with increased temperature. In addition to the formation of linear ethers, isomerisation of the carbocation can lead to formation of branched ethers from linear alcohols when C ⩾ 3. Isomerised ether formation can occur *via* nucleophilic attack by an *n*-alcohol on either a rearranged carbocation or by direct attack on an alkene formed by the dehydration reaction. However, we did not detect any secondary alcohols, which could be formed from the hydrolysis of the rearranged carbocation intermediate. This suggests that branched ether formation by the reaction of a secondary with a primary alcohol was unlikely under our conditions. Neither were any products from two secondary alcohols reacting together detected, providing additional evidence that hydrolysis of the carbocation intermediate was not occurring.

Fig. 7 shows that the formation of isomerised ethers decreases with increasing carbon chain length and with a corresponding increase in the formation of alkenes. This result is consistent with our previous observations,[32] but it is only in the new automated reactor that the formation of propene and butene can be quantified.

Given the formation of multiple products, it becomes increasingly difficult to make a meaningful comparison of the effect of pressure on the reactions of higher alcohols.

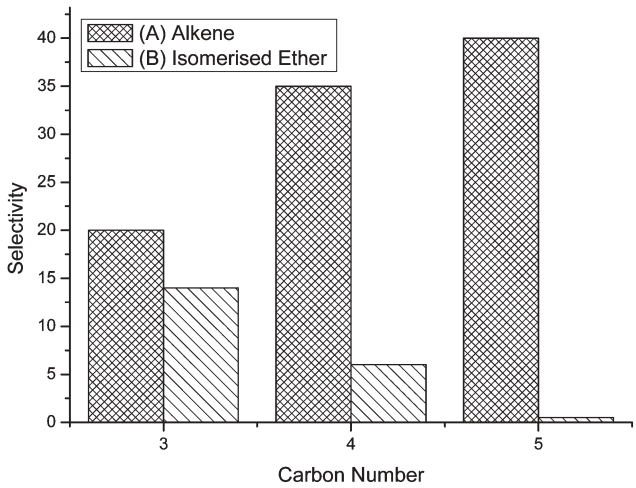


Fig. 7 Change in selectivity towards alkene (A) and *n*-alkyl iso-alkyl ether (B) for C > 2 *n*-alcohols at 220 °C. On increasing carbon chain length the selectivity for the dehydration of the *n*-alcohol increases, whilst the selectivity to branched ethers decreases.

However, direct comparisons of the effect of pressure on conversion to linear ethers at 220 °C can be made by normalising the results at 220 °C and 100 bar. Thus, Fig. 8a shows the normalised yield of linear ethers for C_1 to C_4 at pressures from 100 to 350 bar at 220 °C. The figure shows that pressure affects the yields of the individual reactions differently. All reactions studied show a significant decrease in conversion between 100 and 150 bar, with EtOH and MeOH showing the largest falls. On increasing the system pressure further, the conversion of both MeOH and EtOH increase. On the other hand the yield of $(n\text{-Pr})_2O$ is largely unaffected at higher pressures, whereas the yield of $(n\text{-Bu})_2O$ continually decreases. At 350 bar, the conversions of MeOH and EtOH to

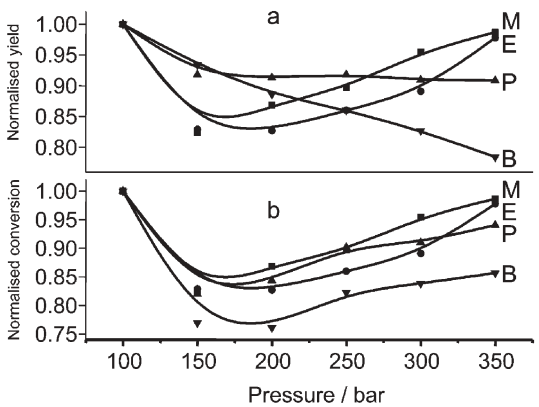


Fig. 8 (a) The effect of pressure on yield of linear ethers at 220 °C normalised to 100 bar. (b) The effect of pressure on the conversion of alcohols to both ethers and alkenes at 220 °C normalised to 100 bar. Increasing the pressure above 150 bar shows a general increase in the conversion, this is probably due to increases in residence time. The traces are labelled (M) MeOH (E) EtOH (P) *n*-PrOH (B) *n*-BuOH. This is a slightly unconventional approach, but it is equivalent to the more common strategy of using multiple ordinate scales, which would be somewhat confusing in a case such as this when there are so many different products.

Me_2O and Et_2O are comparable to those at 100 bar; whereas the yields of $(n\text{-Pr})_2O$ and $(n\text{-Bu})_2O$ are markedly lower at high pressure.

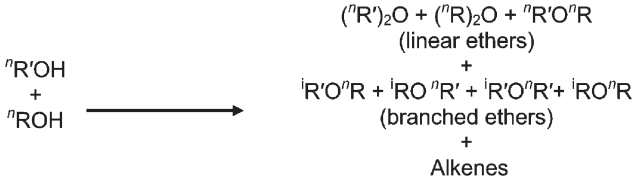
Fig. 8b shows the normalised conversion of the alcohols (*i.e.* to both ethers and alkenes). Unlike Fig. 8a, the curves in Fig. 8b are surprisingly similar. Therefore, the difference between Fig. 8a and Fig. 8b is merely a reflection of the change in selectivity between the different products. The overall 'U' shape of the curves in Fig. 8b is probably connected to a switch in the phase of the reaction mixture from biphasic at low pressure to monophasic at high pressure. However, the formation of H_2O as one of the reaction products makes a comprehensive phase analysis extremely difficult.

Thus, we believe that the overall pressure plays only a small role in the final product selectivity of branched ethers *versus* alkene gases. By analogy with Me_2O (above) it is probable that the outcome of these reactions is largely controlled by mass transport and the inherent selectivity of the catalyst rather than the properties of $scCO_2$ itself.

iii) Etherifications involving two different alcohols

In this section we report the results of etherification of two alcohols simultaneously with the aim of generating unsymmetrical ethers. None of our earlier experiments involved the quantification of reaction rates. Therefore we had no *a priori* means of predicting the yield of unsymmetrical ethers, ROR′, compared to those of R_2O and R'_2O. However, if the rates of etherification were essentially independent of the alcohols then, in the reaction of MeOH + EtOH, one might expect a 50% yield of the unsymmetrical ether, MeOEt, and 25% yields of each of the symmetrical ethers, Me_2O and Et_2O. For reactions involving the higher ethers, the situation is somewhat more complicated because of the possibility of forming branched ethers from *n*-alcohols and also there is the problem of alkene formation, Scheme 1. In some cases chromatographic resolution of all components cannot be achieved by employing a single chromatographic method. It is possible however, to split the injected sample onto two different analytical columns and/or detect by two different methods. In the examples reported in this paper, two different single analytical columns were used, depending on the reaction and the products obtained.

Table 2 and Table 3 summarise the results from a series of experiments with pairs of alcohols. A number of points are clear. Firstly, the selectivity for MeOEt was almost exactly 50%, as expected from Scheme 1. Secondly, ignoring the formation of branched ethers, the selectivity for most of the unsymmetrical ethers was also close to 50%; none was lower than 42%. Therefore, somewhat surprisingly, the selectivity in



Scheme 1 All possible products from the simultaneous etherification of two different alcohols with more than two carbon atoms.

Table 2 The average yields at 220 °C for various symmetrical ethers formed from etherification reactions involving pairs of alcohols. Values in bold are for symmetrical ether formation from reactions involving a single alcohol

Alcohol Product	MeOH Me_2O (%)	EtOH Et_2O (%)	*n*-PrOH $(n\text{-Pr})_2O$ (%)	*n*-BuOH $(n\text{-Bu})_2O$ (%)	*n*-PntOH $(n\text{-Pnt})_2O$ (%)
MeOH	**10.5**	3.9	2.8	11.0	6.3
EtOH	1.1	**25.4**	5.1	8.5	4.5
n-PrOH	—[a]	5.4	**26.0**	7.4	7.4
n-BuOH	—[a]	8.2	7.1	**26.3**	5.8
n-PntOH	—[a]	4.2	4.5	4.9	**18.3**

[a] Chromatographic separation of Me_2O from alkene gases was not possible.

nearly all these reactions was close to statistical. Of course, these selectivities were calculated ignoring formation of alkenes. Indeed, the absolute yield of unsymmetrical ethers of the higher alcohols was relatively modest and not necessarily encouraging as the basis for green chemical processing.

This near-statistical distribution of ethers could arise in three different ways: (i) all the reaction rates could be essentially equal, (ii) ethers once formed could be re-hydrolysed to regenerate the alcohols leading to a statistical mixture, provided that the residence time in the reactor was long enough to establish equilibrium, or (iii) a trans-etherification reaction could be occurring in which a symmetrical ether reacts with an alcohol to generate an unsymmetrical ether. Earlier in this paper we showed that different alcohols gave different yields of ethers under similar conditions, which suggests that the rates of all these reactions are unlikely to be equal. Thus, in the next section, we attempt to distinguish between the possibilities of re-hydration and trans-etherification.

iv) Acid-catalysed reactions of ethers with alcohols

In an initial experiment, Et_2O was passed over Amberlyst 15 at 150 °C and 100 bar CO_2 in the absence of any water or additional alcohol. The ether was not stable under these conditions. Analysis of the mixture downstream showed C_2H_4, 39%, and EtOH, 8%, with the mass balance of 53% Et_2O. This result is initially surprising because the decomposition of Et_2O would be expected to lead to equimolar quantities of EtOH and C_2H_4. However, under the conditions of this experiment, any EtOH formed could react with itself to regenerate Et_2O,

Table 3 The average yield of unsymmetrical ethers formed in reactions involving pairs of alcohols. Values in bold show the absolute yields of unsymmetrical ethers. Values in italics show the selectivity to unsymmetrical ethers, ignoring the formation of alkenes and small quantities of iso-ethers

Unsymmetrical ethers	MeOR (%)	EtOR (%)	*n*-PrOR (%)	*n*-BuOR (%)	*n*-PntOR (%)
MeOH	—	**5.2**	**5.7**	**19.1**	**11.2**
EtOH	*51.0*	—	**9.6**	**12.2**	**8.9**
n-PrOH	—[a]	*47.8*	—	**11.7**	**12.2**
n-BuOH	—[a]	*42.2*	*44.7*	—	**11.3**
n-PntOH	—[a]	*50.6*	*52.8*	*51.4*	—

[a] Insufficient analytical data to elucidate selectivity.

which in turn could decompose. Thus, the outcome from this series of reactions is the accumulation of C_2H_4 and H_2O.

Next, a reaction involving a 1 : 1 mixture of Et_2O and *n*-PrOH was performed. The yield followed a similar trend to the majority of etherification reactions reported in this paper, with changes in temperature producing the largest effect on conversions and pressure showing modest influence. A 10% yield of the unsymmetrical ether, *n*-PrOEt, was found at 220 °C and 350 bar. This is virtually identical to the yield from the reaction of EtOH and *n*-PrOH, Table 3. This observation strongly favours a mechanism in which Et_2O is hydrolysed into EtOH prior to formation of *n*-PrOEt rather than a formal 'trans-etherification'. This conclusion is further supported by the observation that at 220 °C the selectivity for *n*-PrOEt over $(n\text{-Pr})_2O$ increased linearly from approximately 0.8 : 1 at 100 bar to 1.6 : 1 at 350 bar. Increased pressure will give increased residence time with a corresponding increased decomposition of Et_2O. Furthermore, free EtOH was detected in small quantities in the product stream. Unfortunately, the presence of C_2H_4 could not be confirmed in this experiment because separation of the gaseous products, ethene and propene, was not possible using our chromatographic method and if a different more suitable method had been used the ethers could not have been easily quantified.

Finally the reaction of di-isopropyl ether, $(i\text{-Pr})_2O$, with *n*-PrOH was carried out over Nafion SAC-13. Although the unsymmetrical product *n*-PrO*i*-Pr, is identical to the branched product from the etherification of *n*-PrOH, a change in selectivity of this product would indicate a chemical interaction between *n*-PrOH and $(i\text{-Pr})_2O$. Table 4 shows that formation of *n*-PrO*i*-Pr followed similar trends in conversion to those of *n*-PrOEt, above. The yield of *n*-PrO*i*-Pr was much higher than from the etherification of *n*-PrOH alone, indicating that $(i\text{-Pr})_2O$ is involved in the reaction. Perhaps the most telling feature is that most of the $(i\text{-Pr})_2O$ was destroyed in the reaction and more propene was formed than could have been generated from the *n*-PrOH which was fed into the reactor.

Conclusions

In this paper we have for the first time quantified the acid-catalysed etherification of MeOH and EtOH in $scCO_2$. We have measured the branching ratio between etherification and alkene formation for alcohols up to C_5 and have investigated the formation of unsymmetrical ethers during the co-etherification of two different alcohols. Most surprisingly, the selectivity for unsymmetrical ethers is close to 50% for all alcohols studied, suggesting that the product distribution for most of the reactions is close to statistical.

Table 4 The product distribution from the reaction of $(i\text{-Pr})_2O$ with *n*-PrOH at 220 °C over Nafion SAC-13

Pressure/ bar	Propene (%)	*i*-PrOH (%)	*n*-PrOH (%)	$(i\text{-Pr})_2O$ (%)	*n*-PrO*i*-Pr (%)	$(n\text{-Pr})_2O$ (%)
100	52.6	3.9	14.8	7.2	18.1	3.5
150	50.3	4.4	15.0	8.1	19.1	3.0
200	50.5	4.6	14.2	7.6	20.4	2.8
250	50.2	4.9	13.9	7.4	21.0	2.7

We believe that we have demonstrated a higher level of automation than has previously been achieved for $scCO_2$ flow reactors in routine laboratory use. This new apparatus significantly increases the number and scope of experiments that can be performed in $scCO_2$ flow systems. It opens up the possibility of conducting systematic and detailed studies which can be supported by statistically large sets of high quality data. By direct sampling, it is now possible to detect and analyse all of the gaseous products, which might be lost in the expansion system of more traditional flow reactors.

We believe that the optimal strategy for green chemistry in SCFs will be a combination of automated reactors and smaller volume, manual apparatus. The simpler apparatus has the versatility required for rapid exploratory experiment while the automated reactor can provide the detailed, precise data needed for larger scale implementation of the reactions. In the longer term, automation opens the way to high throughput supercritical reactions for faster process development.

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Continuous-flow, gas phase synthesis of 1-chlorobutane (1-bromobutane) from 1-butanol and aqueous HCl (HBr) over silica-supported quaternary phosphonium salt

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The continuous-flow syntheses of 1-chlorobutane and 1-bromobutane were achieved in the gas phase starting from 1-butanol, at 130–170 °C and atmospheric pressure. An aqueous mixture of 1-butanol and commercial hydrochloric or hydrobromic acids (37 and 48%, respectively) was fed into a plug-flow catalytic reactor loaded with zinc chloride ($ZnCl_2$: 5 and 15 wt%) or a phosphonium salt (n-$Bu_4P^+Br^-$: 5 and 15 wt%), both supported on silica gel. Overall yields in butyl halides ranged from 87 to 30%, with weight hourly space velocity (WHSV) up to 0.53 h^{-1}. The onium salt allowed a high reaction selectivity, since no transposition products were observed. In the presence of a molten phase composed of the onium salt, a S_N2 nucleophilic substitution takes place. The reaction mechanism is discussed.

Introduction

Gas–liquid phase transfer catalysis (GL-PTC)[1a,b] is a method of synthesis which, operating under continuous-flow (c.-f.) conditions, allows nucleophilic displacements to be performed under anionic activation. The phase transfer (PT) catalyst increases the anion activity, providing a scarce solvation to the anions. Gas phase synthesis is possible thanks to the fact that the catalyst is present in a molten state and usually coats an inorganic support with a liquid film.

GL-PTC is related to the general class of supported liquid phase catalysis (SL-PC) processes;[2a,b] in this regard, significant industrial examples are the UOP processes (supported phosphoric acid),[3a,b] the Deacon catalysts (ethylene oxychlorination),[4] the liquid detoxification from polychlorinated biphenyls (supported polyethylene glycols on potassium carbonate),[5] *etc*.

Since the development of ionic liquids (IL),[6a–c] the importance of using a proper liquid phase has been widely recognized; however, there is no conceptual difference between IL-performed reactions and those carried out under SL-PC (or GL-PTC) conditions, since in both cases the reaction occurs in a similar environment: a liquid phase constituted by the catalyst/solvent, which often is an organic or inorganic salt.

GL-PTC provides four known types of catalysis in which anion activation is involved. The first two cases operate with reactive beds; while real catalytic beds promote the reaction in the last two instances.[1] From a practical point of view, under GL-PTC conditions an immobilized PT catalyst (onium salts, polyethylene glycols, crown ethers, *etc.*) coats an inert support (by impregnation or by grafting); the latter in its turn is loaded on a plug-flow reactor.[7] The reaction is carried out in the gas phase and the products are continuously collected at the end of the reactor.

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Operating with a plug-flow reactor, the reactions involving dimethyl carbonate (DMC) as reagent show particular relevance;[8] when carried out in the presence of a base as co-catalyst, such processes allow DMC (a green reagent) to be converted into a large number of products, with high rate and selectivity.

Nucleophilic displacements operating in acidic media under GL-PTC condition are here reported and deal with the transformation of primary alcohols into the corresponding chlorides or bromides. Actually, the synthesis of alkyl halides from primary alkyl alcohols poses no major synthetic difficulties, and a large number of direct methods are reported.[9] However, they react slowly with aqueous hydrochloric acid, unless a Lewis acid catalyst is present (*e.g.* $ZnCl_2$).[10] It is well known that the Lucas test discriminates between primary, secondary, and tertiary alcohols, since only the latter reacts according to an S_N1 mechanism. On the contrary, if a PT catalysis is used,[11] an S_N2 mechanism operates. Moreover, PT catalysis is a viable method only for the conversion of water-insoluble primary alcohols: under liquid–liquid PT conditions, the quaternary onium salts extract HCl (HBr) acid into the organic phase;[11] as a consequence, water-soluble alcohols do not react.

Recently, the transformation of fatty alcohols to alkyl halides was achieved using *para*-toluene sulfonic acid as catalyst. The ionic liquids 1-octyl-3-methylimidazolium halides ([omim]X, X = Br, I)[12] were used both as reagents and solvents. This method utilizes the counteranion of the IL as the nucleophile and is applicable to fatty alcohols only. Alkyl chlorides are not obtainable under such conditions.

Results

Here we report the transformation of water-soluble primary alcohols using aqueous hydrochloric acid: 1-butanol can be catalytically transformed into the corresponding chloride or bromide, operating under GL-PTC conditions, by a c.-f.

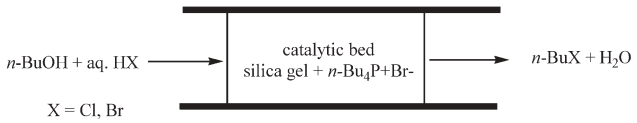

Fig. 1 Continuous-flow synthesis of 1-chlorobutane and 1-bromobutane in a plug-flow reactor.

method. The aqueous solution of alcohol and HX (X = Cl, Br) is run through a plug-flow reactor heated at 130–170 °C and loaded with silica supported tetra-*n*-butylphosphonium bromide (*n*-$Bu_4P^+Br^-$, mp = 102–104 °C, stable at high temperature) or zinc chloride ($ZnCl_2$). In the catalytic column, the reagents flow through the supported catalyst in the gas phase at atmospheric pressure (Fig. 1).[13]

When the reaction takes place, two phases are collected, since the alkyl halides are scarcely soluble in water. A series of experiments was carried out by feeding a 1 : 3 v/v aqueous solution of 1-butanol and HCl at atmospheric pressure; the catalytic bed, the flow rate, and the temperature were changed (see Table 1).

Catalytic activity was determined by analyzing the reaction mixture resulting from 40.0 ml of reactant mixture, under steady state conditions. Weight hourly space velocity (WHSV) gives the efficiency of the catalytic bed; turnover frequency (*N*) describes the catalytic activity of the catalyst.[14]

$ZnCl_2$ proved to be an active catalyst: the highest efficiency was obtained at 150 °C and with a relatively fast flow rate (140 ml h^{-1}; entry 3). Under such conditions, the catalytic bed showed the highest efficiency with a WHSV of 0.41 h^{-1}: the product 1-chlorobutane could be isolated with a 53% overall yield. The increase of the reaction temperature and/or the decrease of the flow rate (170 °C and 30 ml h^{-1}, respectively: entry 2), favored the formation of by-products lowering the overall yield of 1-chlorobutane to 30%. On the contrary, by reducing the reaction temperature (130 °C) and with a higher flow rate time (50 ml h^{-1}), pure 1-chlorobutane could be collected (86%), though both the overall yield and the bed efficiency dropped (47% and 0.13 h^{-1}, respectively, entry 4).

Under the same reaction conditions as entry 3, the increase in the amount of the active phase ($ZnCl_2$, 15%: entry 5) did not improve the purity of the product; however, the bed efficiency increased to 0.53 h^{-1}.

A better comparison between the efficiency of the two different catalysts is given by the turnover frequency *N*. As expected, *N* increases as temperature increases and decreases with the load of the catalyst. More interestingly, *N* is higher for the phosphonium catalyst rather than $ZnCl_2$ catalyst, the classical promoter of such transformations.

The use of *n*-$Bu_4P^+Br^-$ as catalyst allowed a higher reaction selectivity with respect to $ZnCl_2$: in all cases very pure 1-chlorobutane could be obtained (83–95%, entries 6–7) even operating at an elevated temperature (170 °C) and with a flow rate of 21 ml h^{-1} (entry 7).

When compared with $ZnCl_2$ under the same reaction conditions (entries 2 and 6), the higher selectivity achievable with the onium salt compensated its lower activity. In particular, a five-fold increase of the *n*-$Bu_4P^+Br^-$ load (entry 7), allowed the recovered organic phase to approach the theoretical yield (10.3 g *vs.* 11.2 g, 87.5% overall yield; this difference is mainly attributable to deficiency in condensation, due to the volatility of 1-chlorobutane).

The organic phase of entry 7 was constituted of the desired product 1-chlorobutane (95%) and contains 5% of dibutyl ether. It had a bp of 77 °C and $n^{20}{}_D$ = 1.4030 (Lit[15]: bp 78.4; $n^{20}{}_D$ = 1.4021).

The procedure can be extended to the synthesis of alkyl bromides as well. By flowing a mixture of 1-butanol and 48% aqueous HBr (1 : 3 molar ratio) through 50 g of a catalytic bed made of 15% $ZnCl_2$ or 15% *n*-$Bu_4P^+Br^-$ on silica gel, at 140 °C and 140 ml h^{-1}, the resulting organic phase constituted of 1-bromobutane. The good yields (95% in the case of $ZnCl_2$ and 98% in the case of onium salt) reflect the higher reactivity of the bromide anion.[4]

Table 1 Continuous-flow reaction of 1-butanol with aq. HCl (35%) in the presence of silica gel-supported catalysts[a]

					1-Chlorobutane				
	Catalytic bed/g	Reagent flow[b]/ml h^{-1}	*T*/°C	Recovered organic phase/g[c]	(%)[d]	Isolated yield/g[e]	Overall yield (%)[f]	WHSV[g]/ g h^{-1} $g_{cat}{}^{-1}$	$N \times 10^4/s^{-1}$[h]
1	Silica gel[a] (50)	30	170	0	—	—		—	—
2	$ZnCl_2$, 5% (50)	30	170	6.6	50	3.3	29.5	0.050[i]	4.0
3		140	150	7.6	78	5.9	52.7	0.413	34
4		50	130	6.1	86	5.3	47.3	0.133[j]	11
5	$ZnCl_2$, 15% (50)	140	150	9.8	78	7.6	67.9	0.532	14
6	*n*-$Bu_4P^+Br^-$, 5% (50)	30	170	2.9	83	2.4	21.4	0.036	7.4
7	*n*-$Bu_4P^+Br^-$, 15% (250)	21	170	10.3	95	9.8	87.5	0.021	1.4

[a] All reactions were carried out at atmospheric pressure by using a mixture of 1-butanol and aq. HCl in a 1 : 3, v/v ratio. Silica gel and silica gel coated with *para*-toluene sulfonic acid or polyethylene glycols as catalysts were completely inactive. [b] Total volume of the reagents fed through the plug-flow reactor, measured after equilibrating the system by pre-feeding 10 ml of reagent mixture. [c] Recovered by condensation and phase separation at the outlet of the reactor. [d] % by GC of 1-chlorobutane in the organic phase; other products were alkenes (elimination) and 2-butanol and *iso*-butanol (isomerization). [e] Some HCl was dissolved in the recovered organic phase; the reported yield was not corrected for it. Theoretic yield, 11.2 g of 1-chlorobutane. [f] Overall yield = isolated yield/11.2 (theoretical yield of 1-chlorobutane). [g] Efficiency of the bed. [h] Turnover frequency, efficiency of the catalyst. [i] As a rule, when $ZnCl_2$ is used, about 10% isomeric butenes and 10% 2-butanol are collected as by-products. Trace amounts of dibutyl ether were observed when the catalyst was a PT agent. [j] By feeding the exhausted aqueous phase deriving from entry 4 and containing unreacted 1-butanol, under the same conditions, 3.0 g of organic phase were collected from 40.0 ml of reagent mixture. This organic phase showed the same content of 1-chlorobutane (78%) and by-products.

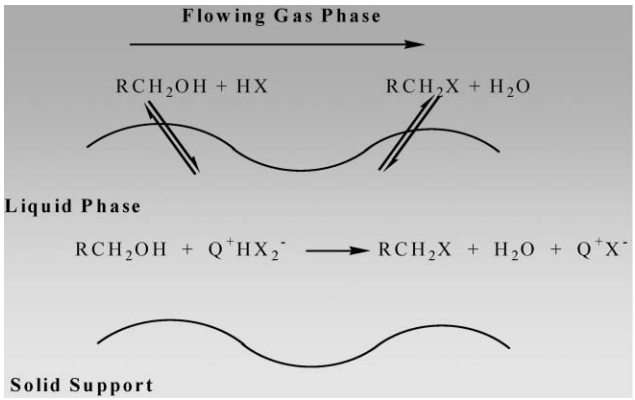

Fig. 2 Conversion of primary alkyl alcohols into primary alkyl halides under GL-PTC conditions.

Discussion

The described process is an example of GL-PTC. In fact, the phosphonium salt constitutes a supported liquid film of catalyst which promotes anion exchange between the halide and 1-butanol.

The presence of the PT catalyst shifts the mechanism from mixed S_N1/S_N2 operating with $ZnCl_2$, catalyst, to pure S_N2.[16a,b]

The formed hydrogen-bonded adduct, $R_4P^+ HX_2^-$, was the active intermediate, so avoiding isomerization and elimination by-products, and promoting excellent chemoselectivity to the primary alkyl halide (Fig. 2).

The mechanism involves protonation of the alcohol, followed by the attack of the chloride nucleophile. The by-product dibutyl ether forms by the same mechanism, without carbocation intermediates, as shown in Scheme 1.

Recently, the concept of SL-PC has been revisited, along with the introdution of IL as innovative green solvents for organic synthesis. In particular the acronyms SILC (Supported Ionic Liquid Catalysis)[17] and SILP (Supported Ionic Liquid Phase)[18] have been coined to describe a homogeneous metal catalyst confined on the surface of an inert support by a film of an ionic liquid, such as for example [bmim][PF_6] or [bmim][n-$C_8H_{17}OSO_3$]. In both cases a Rh-diphosphine catalyst was dissolved in the ionic liquid and immobilized on silica. The catalysts were then used for the batch hydrogenation of a series of C_6 olefins, and for the continuous fixed-bed gas phase hydroformylation of propene, respectively. Noticeably, this is not a novel concept in hydroformylation reactions, since c.-f. procedures were investigated by Sholten and his co-workers, who extensively reported the effect of the nature of the support and the liquid phase on the hydroformylation of propene.[19a–d]

Conclusions

This method is a further application of GL-PTC and might be of interest for the conversion of low molecular weight, water-miscible, alcohols to the corresponding alkyl halides. The continuous-flow conditions, along with no use of solvents, make this method intrinsically green: the reaction is truly catalytic because the catalytic bed is not consumed, the catalyst and the recovered aqueous phase can be recycled (see Experimental), enriched in HX, and reused without treatment, the only by-product is water.

Primary alcohols like 1-propanol or allyl alcohol react in the same way as 1-butanol, while secondary alcohols give predominantly transpositions and elimination derivatives, because the prevailing mechanism proceeds through a carbocation.

Experimental

All used compounds were ACS grade and were employed without further purification.

GC analyses were performed using a 30 m, CP-sil 24 CB capillary column. Reaction mixtures were compared with authentic commercial samples. Masterflex mod. No. 7013 was used as peristaltic pump.

Preparation of silica gel-supported catalyst

Silica gel (chromatography grade, Merk Art. No. 7734, Kieselgel 60, 70–230 meshes, pore diameter 60 A, specific surface area 500 $m^2\ g^{-1}$) was added in desired amounts (5 or 15% w/w) to $ZnCl_2$, or n-$Bu_4P^+Br^-$ dissolved in methanol. The solvent was removed by evaporation and the support heated in a oven at 100 °C for 15 h.

Synthesis of 1-chlorobutane

A mixture of 12.5 ml of 1-butanol in 37.5 ml of 35% aqueous HCl was fed to a 400 mm long plug flow reactor (90 ml total volume), kept at 150 °C by a thermostat, and loaded with 50 g (or 150 g with a plug-flow reactor of 250 ml total volume) of the silica-supported catalyst; constant flow rates were maintained by the metering pump. At the outlet of the reactor the products were condensed (those originated by the first 10 ml of feed were discarded since they contain a small amount of 1-bromobutane and so the catalyst is transformed into n-$Bu_4P^+Cl^-$, mp 62–66 °C).

The binary phase mixture was collected, the organic phase was separated, weighed, and analyzed by gas-chromatography. Distillation yielded the pure product. No additional workup was necessary.

The aqueous phase containing exhausted HCl and unreacted 1-butanol could be recycled in the same reactor without other

Scheme 1

treatments. In fact, the catalytic bed could also be reused without loss of activity, as was demonstrated in one case by feeding the residual aqueous phase through the used catalytic bed (see footnote i, Table 1).

After the feeding of 500 ml of 1-butanol and 35% aq. HCl (onium salt catalyst), no deactivation of the catalytic bed was observed, and the collected reaction mixtures had the same composition.

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The influence of room-temperature ionic liquids on the stereoselectivity and kinetics of the electrochemical pinacol coupling of acetophenone

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The electrochemical pinacol coupling of acetophenone is performed in three ionic liquids, [BMIM][NTf_2] (1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide), [Me_3BuN][NTf_2] (trimethylbutylammonium bis(trifluoromethylsulfonyl)imide), and [Et_3BuN][NTf_2] (triethylbutylammonium bis(trifluoromethylsulfonyl)imide). Besides the high operational simplicity of electrolysis in ionic liquids and particularly the ease of product recovery, as compared to conventional electrolytes, ionic liquids are also demonstrated to exert strong effects on both the stereoselectivity and kinetics of the reaction. Because ion associations occur between the radical anion intermediates and the ionic liquid cations, the dimerization step is considerably facilitated. Depending on the strength of the ionic interactions, the stereoselectivity or the kinetics is increased.

Introduction

Because pollution prevention has been shown to be much more efficient than remediation in terms of costs and risks, chemists now strive to develop eco-friendly processes as reflected by the various approaches described in the recent literature. In this context, electrosynthesis remains an attractive method since the electrons are "clean" and cheap reagents which limit the formation of side-products. Despite i) these obvious advantages, ii) the ability to control a large range of chemical processes at electrodes and iii) the fact that electrochemical engineers have proposed many advances to improve electrochemical processes towards the industrial-scale, only a few organic electrochemical routes have been developed at preparative scale.[1] The major reason for this lack of industrial enthusiasm for electrochemical processes comes from the concomitant use of organic solvents (THF, DMF, DMSO, acetonitrile, *etc*…) with organic electrolytes to perform electrosynthetic processes, and the difficulty in separating the product from the complex electrolyte media. An alternative medium to circumvent this problem could be found in room-temperature ionic liquids (RTILs).

RTILs are salts that are liquids at room temperature and mainly consist of a combination of bulky organic cations (*N*,*N*-dialkylimidazolium, quaternary ammonium,…) with common weakly coordinating anions ($AlCl_4^-$, BF_4^-, PF_6^-, $CF_3SO_3^-$, $(CF_3SO_2)_2N^-$, *etc.*). They have been demonstrated to be good alternative reaction media to organic volatile solvents in various chemical processes thanks to their attracting physical and chemical properties (stability at high temperature, negligible vapor pressure, non-flammable, non-volatile, ability to dissolve a wide range of organic and inorganic compounds…).[2] In electrochemistry, RTILs were considered as versatile electrolytes for diverse technologies such as electroplating of base metals, batteries, photovoltaic devices, fuel cells, organic electrosynthesis.[2,3] Indeed, RTILs display attractive electrochemical properties from an electrosynthetic perspective. They are extremely redox-robust. Thanks to their inherent ionic conductivity, they can be used as solvents for electrochemical applications without the need of adding any supporting electrolytes that normally would have to be recovered/recycled after electrolysis. Of course, RTILs do exhibit also a number of distinct properties that can be considered electrochemically disadvantageous such as larger viscosities or lower ionic conductivities than those exhibited by conventional electrolytic media.[4]

However, the high versatility of ionic liquids regarding the ease of product recovery,[5] their ability to recycle and the tailoring of these specific solvents for a given use (selectivity of a reaction, for instance[6]) may compensate for their drawbacks in the adoption of RTILs in real electrosynthetic processes.

Actually, the transfer of potentially useful electrochemical reactions (in terms of commercial-scale) from conventional molecular electrolytic media to a RTILs medium may be not straightforward and the specific nature of the RTILs is expected to affect the reactivities of electrogenerated species, especially in the case of charged reactants. Modifications of electron-transfer rates or reaction kinetics involving radical ions have been detected using pulse radiolysis techniques[7] or photochemical methods.[8] We, therefore, initiated a program aimed at studying how the use of ionic liquids can adversely influence the kinetics and the nature of mechanisms involving electrogenerated radical ions.[9]

In a former work, we found large modifications of the cleavage reactivities of chlorinated radical anions when shifting from an organic molecular solvent to an ionic liquid.[9b] These modifications resulted from an ion pairing-like solvation effect and were mainly dependent on the charge localization in the radical anions: the strongest effect was observed for the 4-chlorobenzophenone radical anion, where the negative charge is concentrated on a small portion of the molecule. In this case, we observed a change in mechanism where coupling

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overruns the usually-observed cleavage reaction, due to a strong stabilisation of the generated radical anions in the ionic liquids.

In the present work, we describe the effects exerted by three different ionic liquids, [BMIM][NTf_2] (1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide), [Me_3BuN][NTf_2] (trimethylbutylammonium bis(trifluoromethylsulfonyl)imide0, and [Et_3BuN][NTf_2] (triethylbutylammonium bis(trifluoromethylsulfonyl)imide) on the kinetics and selectivity in the electrochemical pinacol coupling of acetophenone.

Pinacol coupling of ketones or aldehydes give rise to the formation of 1,2-diols that are useful synthons in various organic syntheses such as, for instance, intermediates for the preparation of biologically important molecules. The pinacolization of aromatic carbonyl compounds can be achieved from the electroreduction of the corresponding carbonyl compounds. The overall electrochemical process results in a competition between pinacol and alcohol formation.[10,11] Varying amounts of these two products were usually obtained, strongly depending on the nature of the electrolytic medium used.

Results and discussion

Electrochemical behaviour of acetophenone in ionic liquids—Comparison with acetonitrile (ACN) + 0.1 M Bu_4NPF_6 conventional electrolyte

Fig. 1 displays a typical cyclic voltammogram of the reduction of acetophenone in ionic liquids. In the three ionic liquids used in this work, acetophenone exhibits, for a low scan rate (0.2 V s^{-1}), an irreversible wave at −2.3 to −2.4 V *vs.* Fc/Fc^+.[12] Similar patterns can be described for the electrochemical reduction of acetophenone in ACN + 0.1 M Bu_4NPF_6.

As stated above, the electroreduction of acetophenone leads either to the formation of alcohol or to pinacol coupling. There are striking electrochemical differences between the two pathways since the formation of alcohol involves the transfer of two electrons and two protons (per molecule of acetophenone) while the pinacol coupling requires one electron and two protons (per molecule of acetophenone). The number of electrons exchanged have been determined, both in ACN and ionic liquids, from comparison of the height of the irreversible wave to the reversible wave of ferrocene under the same conditions, neglecting the slight variation in diffusion coefficient between ferrocene and acetophenone. The variation in the number of electrons exchanged as a function of the initial concentration of acetophenone is diplayed in Fig. 2.

For both media, the stoichiometry of the reaction changes from 2 to 1 when the concentration of acetophenone increases, showing that pinacolization is favored upon increasing the concentration. This result has been often reported in conventional electrolytic media[11] and is consistent with the kinetically second-order nature of a coupling reaction. However, we observed that the number of electrons exchanged becomes equal to 1 in ACN for concentrations of acetophenone ten times higher than the values required in ionic liquids to observe the corresponding change in stoichiometry. This shows that the pinacol coupling is more favored in ionic liquids than in acetonitrile, at least on the time-scale of cyclic voltammetry.

Macroelectrolysis

Macroscale reduction of acetophenone was carried out on a glassy carbon plate in the three ionic liquids at the potentials of the reduction peaks of acetophenone.[13] The electrolysis was followed by cyclic voltammetric analysis using an auxiliary glassy carbon disk electrode. A regular decrease of the height of the irreversible wave of acetophenone is observed, indicating the consumption of the starting acetophenone throughout the macroelectrolysis. Coulometric integration was simultaneously recorded. When the current dropped to about 10% of its initial value, the electrolysis was stopped. For the three ionic liquids, the electrolyses required the consumption of 1 F per mol of acetophenone (Table 1). The electrolysis product was readily separated from the catholyte by simple extraction with diethyl ether. The reduction of acetophenone afforded an almost quantitative yield of acetophenone pinacol (2,3-diphenylbutane-2,3-diol). No alcohol could be detected by NMR or GC-MS analyses. Similar acetophenone pinacol yields have been obtained in conventional electrolytic media under the conditions of using anhydrous aprotic media (DMF or ACN) or alkaline media such as ACN + 14% aqueous 0.1 N KOH or in the presence of 5–10 × 10^{-2} mol L^{-1} small alkali

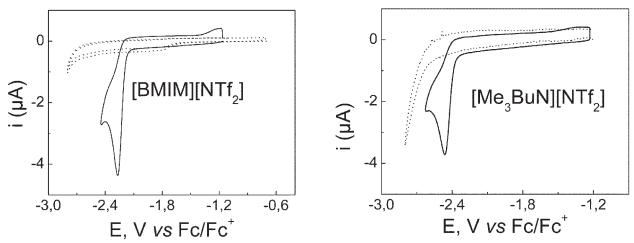


Fig. 1 Cyclic voltammograms of ≈10^{-2} mol L^{-1} acetophenone in [BMIM][NTf_2] and [Me_3BuN][NTf_2] onto a glassy carbon disk electrode at 0.2 V s^{-1}.(—) Background scans of the ionic liquids.

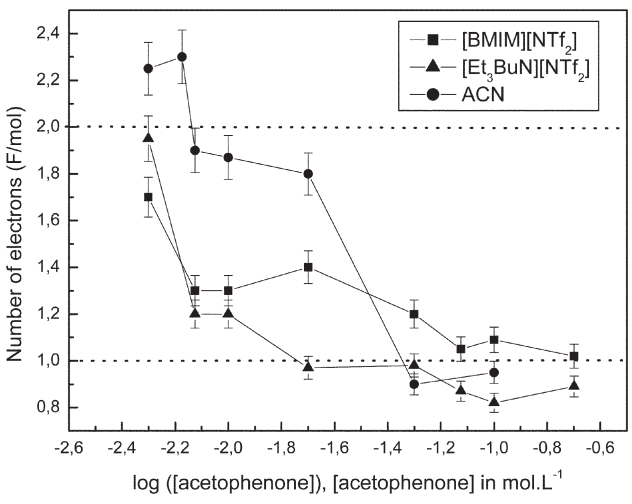


Fig. 2 Variation in the number of electrons exchanged as a function of the concentration of acetophenone for ACN + 0.1 M Bu_4NPF_6, [BMIM][NTf_2] and [Et_3BuN][NTf_2]. Cyclic voltammetry at 0.2 V s^{-1} on a 0.5 mm diameter glassy carbon disk electrode.

Table 1 Preparative electrolysis in ionic liquids

Ionic liquids	Remaining ketone (%)[a]	Electricity consumption/F mol^{-1}	Major product	Yield (%)[b]	D,L/*meso*
[BMIM][NTf_2]	8	1.1	Pinacol	92[d]	1.12 53/47%
[Et_3BuN][NTf_2]	18[c]	1	Pinacol	82[d]	3.74 79/21%
[Me_3BuN][NTf_2]	7	0.97	Pinacol	80[d]	3.3 77/23%

[a] Remaining ketone: remaining amount of ketone/initial amount. [b] Determined by GC. [c] The electrolysis was stopped when the current reached 1/6 of the initial current. [d] For [BMIM][NTf_2] and [Et_3BuN][NTf_2], only pinacol and remaining acetophenone were detected. For [Me_3BuN][NTf_2], 13% of an unidentified side-product was also found by GC-MS.

metal cations.[10e,14] In this context, it is worth emphasizing the operational simplicity of the pinacol coupling in ionic liquids since i) the ionic liquids did not require an extensive drying procedure prior to the electrolysis[15] and ii) the product recovery was easily achieved. Moreover, the residual ether remaining in the ionic liquids after the extraction process was readily removed *in vacuo*. The recovered ionic liquids were then analysed by NMR and cyclic voltammetry. Both analyses showed that the recovered ionic liquids were clean and reusable.

On the basis of ^{1}H NMR[16] and GC-MS analyses, the ratio of *meso* to D,L form in the resulting pinacol was determined. The reduction of acetophenone leads to a mixture of two diastereoisomers, D,L mixture and *meso* compound, in a 1.12 ratio in [BMIM][NTf_2] while this ratio reaches 3.7 and 3.3 in the ammonium-based ionic liquids. Obviously, there is a templating effect toward D,L isomer in the ammonium-based ionic liquids as compared to the imidazolium-based one. The stereochemistry of pinacols is known to be generally controlled by steric and non-steric (H-bonding, electrostatic) interactions between two radicals coupling with each other, and not by interactions with the cathode, because C–C bond formation occurs in the bulk solution.[10d] The nature and the physico-chemical properties (Table 2) of the reaction medium should then affect the product distribution.

The involved radicals are formed by a one-electron transfer and their nature, which strongly depends on the electrolytic medium, can either be a radical anion or a neutral radical (Scheme 1).

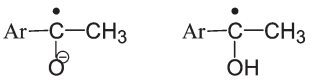
Because the proton availability in the ionic liquids remains very limited, it is likely that the coupling involves radical anions. Moreover, in ionic liquids the anions (and thereby radical anions) are always coordinated to cations. Whilst this could not be properly described as an ion-pair (which implies discrete cation and anion surrounded by molecular solvent), it is not thought likely that the coupling could occur with the uncoordinated radical anion since the solvent shell is ionic. The ion pairing-like solvation effect of ionic liquids that has been described for benzaldehyde[3d] and nitrobenzene derivatives[18] or benzophenone in our former work[9b] strengthens this idea. Hence, the stereoselectivity observed in the ionic liquids can be rationalized as arising by a templating of two radical anions by one or more cations of the ionic liquids. A similar templating effect of radical anions by cations from the supporting electrolyte *via* ion-pair formation has indeed been described in the stereochemistry of the cathodic pinacolisation of acetophenone or its derivatives.[10a,i,19,20] When the cation interacts simultaneously with two radical species, dimerization favors the D,L-product because there are fewer steric interactions, in the corresponding transition state, between groups attached to the reacting radicals (Fig. 3).

Since such ion-pair formations have been evidenced in the case of quaternary ammonium cation-based supporting electrolytes,[10a,i,19,20] it is analogously thought that similar ion-bridging effects occur in the ammonium-based ionic liquids, directing the stereoselectivity of the pinacolization toward the D,L mixture. However, the D,L/*meso* ratio decreases to 1.12 in the imidazolium-based ionic liquids. In this case, we think that ion-bridging is not favoured and an ion-pair is more efficiently formed between the imidazolium cation and one radical anion. This is supported by calculations performed in a former work related to ion-pair formation between benzophenone radical anions and $BMIM^+$, Me_3BuN^+ and Et_3BuN^+ cations.[9b] The calculations have shown that the ion-pair involving the imidazolium cations is more tightly-bound than the corresponding ion-pair with the quaternary ammonium cations. The bulkiness of the quaternary ammonium cation induces a quite large cation–anion distance in the pair that leads to a low electrostatic stabilization, thus favouring

Table 2 Some physico-chemical parameters of ionic liquids

Ionic liquids	Viscosity[a]/mPa s	Density[a]/g mL^{-1}
[BMIM][NTf_2]	69	1.433
[Me_3PrN][NTf_2]	72	1.44
[Me_3HexN][NTf_2]	153	1.33
[Et_3HexN][NTf_2]	167	1.27

[a] From ref. 17, 27.



Scheme 1 Acetophenone-derived transient radicals.

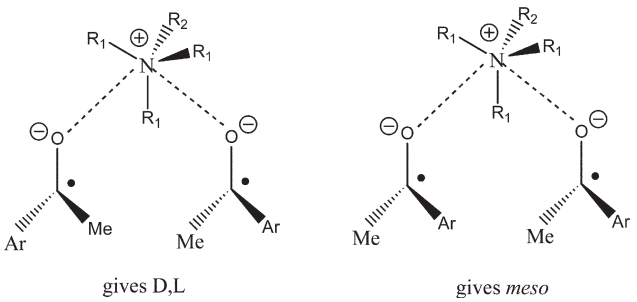


Fig. 3 Steric interactions involved in the case of ion-pair formation between one ammonium cation and two radical anions.

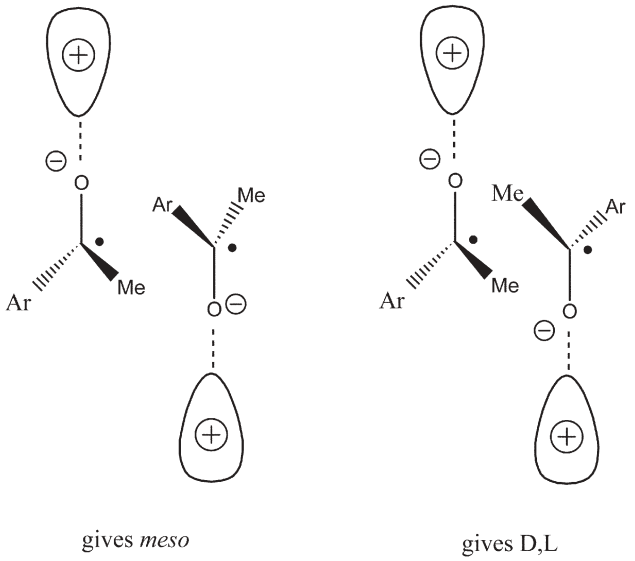


Fig. 4 Steric interactions involved in the case of the formation of a strong ion-pair between an imidazolium cation and an acetophenone radical anion.

ion-bridging. In contrast, the planar geometry of the imidazolium ring allows the oxygen atom of the carbonyl group (that carries the negative charge) to closely face the cationic ring, and thus the cation–anion distance is minimized in the pair. The interaction between the radical anion and the $BMIM^+$ cation is also enhanced by the ability of the imidazolium cation to form an H-bond with the $C^{\bullet}$–O^- of the carbonyl group.[21] Therefore, the interaction between imidazolium cations and acetophenone radicals anions leads to the formation of tightly-bound ion-pairs. The steric interactions of the resulting complex, because strongly hindered, promote a head-to-tail orientation of the two radical anions (Fig. 4). Coupling from this configuration decreases the stereoselectivity of the reaction since both approaches of the radical anions could be identically involved (Fig. 4).

The sterically directing effects of cationic bridging between two coupling anions is greater than the effects between two ion-pairs, explaining the discrepancy observed in the two types of ionic liquid.

Mechanistic aspects and reactivities

Cyclic voltammetry analysis is a powerful tool to study the kinetics and mechanism of a reaction triggered by an electron transfer.[22] The nature of the mechanism involved in the cathodic pinacolisation of acetophenone can be readily determined from the variation of the peak potential, E_p, of the chemically irreversible reduction wave with the scan rate, v, and substrate concentration, c. In the three ionic liquids, analyses of the peak potential as a function of v or c provide linear variations with a slope close to 20 mV per a 10-fold increase in v or close to −20 mV per a 10-fold increase in c. These results indicate that the rate-determining step is a bimolecular coupling process involving two radical anions that formed earlier in a relatively fast electron transfer.[22]

The standard potentials E^0 for the acetophenone/acetophenone radical anion couples were derived as the half-sum between the forward and the backward scans from reversible voltammograms. As seen in Table 3, the E^0 values obtained for ammonium-based ionic liquids are closer to those reported in ACN conventional electrolyte than the E^0 obtained in [BMIM][NTf_2]. A large positive shift for the standard potential of the acetophenone/acetophenone$^{\bullet -}$ is observed in [BMIM][NTf_2]. This result is indicative of the formation of strong ion pairs in [BMIM][NTf_2], as stated above. By comparison, the moderate anodic shift (or no shift) observed in the ammonium-based ionic liquids confirms that the ion pairs are stronger within the imidazolium-based ionic liquids than within the ammonium-based ones.

Concerning the electron-transfer rates, the kinetic parameter $k_s/\sqrt{D}$ was estimated from the peak-to peak separations assuming a Butler–Volmer law and a charge-transfer coefficient $\alpha = 0.5$ (where k_s is the standard heterogeneous rate constant uncorrected from the double layer effect and D the diffusion coefficient taken equal for all species).[22] The k_s values in ionic liquids are lower than those reported in conventional electrolyte, in agreement with our previous studies (Table 3).[9]

The apparent dimerization rate constant (k_{dim}) is determined from comparison of the experimental voltammograms (variation of the reversibility) with calculated curves for different scan rates.[22] As seen in Table 3, the rate constants are quite high in ionic liquids (10^5–10^6) and fall in the same range as those reported in alkaline ethanolic medium. A similar observation has been recently made by Doherty and Brooks for the pinacolic coupling of benzaldehyde.[3d] The kinetics of the cathodic pinacol coupling of benzaldehyde has been widely studied and results showed that the dimerization rate constant is strongly affected by the electrolytic media used : 7×10^5 in alkaline ethanolic medium, 9.5×10^4 in ACN + TEAP, 8.5×10^3 in DMF + TEAP and 2.4×10^3 in sulfolane.[3d,25] The values obtained in the three ionic liquids are much lower (at least one order of magnitude) than the reported values of the diffusion-controlled rate constant,[7a,8c] meaning that the

Table 3 Electrochemical data for acetophenone reductive coupling in ionic liquids and in a conventional electrolyte

	E^0 [a]/V	$\partial E_p(\partial \log v)^{-1}$ / mV dec^{-1}	$k_s(\sqrt{D})^{-1}$/s$^{-1/2}$	D^f/cm^2 s^{-1}	k_s/cm s^{-1}	k_{dim} /L mol^{-1} s^{-1}
[BMIM][NTf_2]	−2.27	23[c]	38	$(1.4 \pm 0.3) \times 10^{-6}$	0.035–0.04	$\geqslant 4 \times 10^6$
[Et_3BuN][NTf_2]	−2.60	20.7[d]	30	$(6.8 \pm 0.4) \times 10^{-7}$	0.02	$3–5 \times 10^5$
[Me_3BuN][NTf_2]	−2.44	25.1[e]	47	$(7.3 \pm 0.4) \times 10^{-7}$	0.035–0.04	$1–2 \times 10^6$
Conventional electrolyte	−2.52[b]	—		1.84×10^{-5}[b]	0.14[g]	2.7×10^5[h]

[a] *vs.* the ferrocene/ferrocenium couple. [b] From ref. 23 in DMF + 0.1 M Bu_4NPF_6. [c] For $v = 0.1$–50 V s^{-1}. [d] For $v = 0.1$–100 V s^{-1}. [e] For $v = 0.1$–500 V s^{-1}. [f] In RTILs, from linear variation $i_p = f(\sqrt{v})$. [g] From ref. 24. [h] In EtOH + 0.1 M Bu_4NOH, ref. 10*b*.

dimerization step should correspond to an activation-controlled process. Therefore, the physico-chemical properties of the solvents such as viscosities should not much affect the mechanism of the reaction. However, in the three ionic liquids, it remains that high dimerization kinetics are observed as compared with those in conventional electrolytes. Actually, in the ionic liquids, the dimerization step is kinetically facilitated from the stabilisation of the radical anions because of their interactions with the ionic liquids cations.[3d,9b] This is also supported by the variation of the k_{dim} values according to the nature of the ionic liquids (Table 3). The apparent dimerization rate constant increases in the order $[Et_3BuN][NTf_2] > [Me_3BuN][NTf_2] > [BMIM][NTf_2]$, which parallels the values obtained for the acetophenone/acetophenone$^{\bullet -}$ formal potential, *i.e.*; $E^{\circ}_{Et3BuNNTf2} < E^{\circ}_{Me3BuNNTf2} < E^{\circ}_{BMIMNTf2}$. In others words, the stronger the ion-pair, the more easily the substrate is reduced, and the faster is the dimerization step. A similar accelerating effect of small cations has been reported, for instance in the case of the cathodic coupling of benzaldehyde and derivatives in aprotic medium containing sodium or potassium salts.[26] The high dimerization rate constant and the accelerating effect observed within the series of ionic liquids can be rationalized as a strong stabilization of the radical anions by ion associations with the ionic liquids cations, *i.e.* the quaternary ammonium cation or the imidazolium cation can accommodate electron density from the radical anion *via* electron delocalisation. Thereby, the coupling of two negatively charged species is considerably facilitated.

Conclusion

The electrochemical reduction of acetophenone at a preparative scale in three ionic liquids ($[BMIM][NTf_2]$, $[Me_3BuN][NTf_2]$, and $[Et_3BuN][NTf_2]$) leads to the exclusive formation of the corresponding pinacol as a mixture of two diastereoisomers, D,L mixture and *meso* compound. The operational simplicity of electrosynthesis in ionic liquids should be emphasized, particularly because of the ease of product recovery with simple extraction.

Besides this technical advantage, the use of ionic liquids was shown to strongly affect the stereoselectivity and kinetics of the pinacolic coupling, depending on the strength of the interactions between the intermediate anion radical species and the ionic liquid cations. Because of the ions association, the dimerization step between the negatively-charged radical acetophenone species is easier. When the acetophenone radical anion is solvated in imidazolium-based ionic liquids, a strong ion-pair occurs and the ensuing charge stabilization allows a fast dimerization step. However, the tightly-bound complex formed from the ion association between the radical anion and the cationic imidazolium species promotes a head-to-tail configuration that decreases the stereoselectivity of the coupling reaction. In contrast, the ion association with the ammonium cations is weaker and the anionic species are less efficiently stabilized, leading to a slower dimerization process. The weakness of the interaction between acetophenone radical anions and ammonium cations is postulated to maximise an ion-bridging formation (one anion with two (or more) cations) as compared to "ion-pair" formation with one anion and one cation. In the latter case, the formation of the D,L diastereoisomer is favoured because the cationic bridging exerts a stronger sterically directing effect between two coupling anions than do two ion pairs.

These results, supported by studies on the cathodic pinacolization of acetophenone as a model reaction, have, in our opinion, a more general impact as they illustrate the interesting and potentially beneficial effect exerted by ionic liquids on charged reactants.

Experimental

Chemicals

The ionic liquids ($[BMIM][NTf_2]$ (1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide), $[Me_3BuN][NTf_2]$ (trimethylbutylammonium bis(trifluoromethylsulfonyl)imide), and $[Et_3BuN][NTf_2]$ (triethylbutylammonium bis(trifluoromethylsulfonyl)imide)) were synthesized from the corresponding bromide or chloride salts *via* a metathesis reaction in aqueous lithium bis(trifluoromethylsulfonyl)imide according to previously published procedures.[4,27] The products were purified by repeated washing with H_2O, filtered over SiO_2 or neutral alumina and dried at 70 °C under vacuum. After being stored for 4–5 days under air (that is, stored without special care), they were used for electrochemical experiments. Just before the experiments, the amount of residual water was measured using Karl–Fisher coulometric titration (Karl Fisher 652 Metrohm) and ranged from 600–800 ppm. Acetophenone was from Acros Organics and used without further purification.

Electrochemical analysis

The electrochemical cell was a classical three-electrode set-up. The counter electrode was a Pt wire, an Ag wire (immersed in HNO_3 65% prior to experiments, then rinsed thoroughly with water and ethanol) was used as a quasi-reference electrode. Ferrocene was added to the electrolyte at the end of each series of experiments, and the ferrocene/ferrocenium couple (E^0 = 0.405 V/SCE in ACN + 0.1 mol L^{-1} Bu_4NBF_4) served as an internal probe.[28] Hence, potential values are given against the ferrocene/ferrocenium couple. The working electrode was a glassy carbon disk of 0.5 mm diameter. The electrode was carefully polished before each voltammetric experiment with 1 μm diamond paste (Struers) and 0.25 μm alumina suspensions (Struers) and ultrasonically rinsed in absolute ethanol. Electrochemical instrumentation consisted of a Tacussel GSTP4 programmer and of a home-built potentiostat equipped with a positive-feedback compensation device.[29] The voltammograms for different scan rates were recorded with a 310 Nicolet oscilloscope. Experiments were performed at room temperature (20 ± 2 °C).

Numerical simulations of the voltammograms were performed with the BAS DigiSim simulator 3.03 (Bioanalytical Systems), using the default numerical options with the assumption of a planar diffusion and a Butler–Voltmer law for the electron transfer. The charge-transfer coefficient, α, was taken as 0.5.

Macroelectrolysis

Experiments were performed with a EGG PAR-173 potentiostat and a EGG PAR-175 universal programmer equipped with a EGG PAR-179 digital coulometer. For each macroscale electrolysis, 1 mmol of acetophenone was electrolyzed at constant potential (at 0.1 V-more anodic potential than the reduction peak potential of acetophenone) in a two-compartment cell. The cathode is a glassy carbon plate (4 cm^2). A SCE electrode with an extension (ACN saturated with Bu_4NPF_6) was used as the reference electrode. The counter electrode is a Pt electrode. The anolyte consisted of electrolyte (ionic liquids) only. An auxiliary glassy carbon disk electrode (1 mm diameter) is used to control (from cyclic voltammetry analyses) the consumption of the starting acetophenone throughout the macroelectrolysis. After the current is dropped to 10% of the initial current, the electrolysis is stopped and 10 drops of water were added to the cathodic solution to protonate the anions. The catholyte is then extracted with three portions of diethyl ether. After removal of ether, the residue is characterized by ^{13}C and ^{1}H NMR and GC-MS. NMR spectra were recorded on a Bruker ARX 200 MHz in acetone-d_6. GC-MS analyses were performed using a Shimadzu GC-14A (FID mode) chromatograph fitted with a 0.25 mm capillary column (optima-240 from Mackerel-Nägel) and a Shimadzu QP-500 quadrupole spectrometer. The analyses were performed using an HP-5973 MSD (EI mode, 70 kV) apparatus (Agilent Technologies). No signal from 1-phenylethanol was found. The racemic : *meso* ratios for the acetophenone pinacol were determined by NMR spectroscopy according to reference 16. GC chromatograms displayed two distinct peaks corresponding to the acetophenone pinacol D,L/*meso* mixture compounds. Peak areas were also used to assess the D,L/*meso* ratios obtained by NMR.

Isolation of acetopenone pinacols were performed in an exemplifying experiment, using more starting materials and ionic liquids. In this experiment, 3 mmol (360 mg) of acetophenone were electrolysed at −2.2 V *vs*. Fc/Fc^+ in 15 mL of [BMIM][NTf_2]. The initial current was 3.8 mA. After the current dropped to 0.3 mA, the electrolysis was stopped and ten drops of water were added to the catholytic solution to protonate the anions. The catholyte was extracted with three portions of diethyl ether (15 mL). The ethereal solution was concentrated *in vacuo* and the pinacol mixture (two diastereoisomers) was separated from the remaining acetophenone by column chromatography (ethyl acetate–hexane as eluent) to yield 239 mg of a white solid (66%).

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Surprisingly high solubility of the ionic liquid trihexyltetradecylphosphonium chloride in dense carbon dioxide

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For the first time an ionic liquid is observed to be appreciably miscible in dense CO_2, up to about 7 mass%. The solubility in CO_2 is more than one order of magnitude higher than for alkanes of similar carbon number. The investigated *P–T* phase behavior of four isopleths for the ionic liquid trihexyltetradecylphosphonium chloride in CO_2 shows a concentration independence of the isopleths for the investigated compositions similar to the known phase behavior of organic compounds such as adamantane, octacosane and squalane in supercritical CO_2 at high pressures. Overall, the results demonstrate that a single-phased ionic liquid–CO_2 solvent system for chemical synthesis is conceivable.

Introduction

Using the two most prominent neoteric solvents ionic liquids and supercritical (sc) CO_2 combined as a medium for chemical synthesis[1–8] including biosynthesis[9,10] is receiving increased attention. This interest has been sparked by the initial observations that CO_2 is relatively soluble in imidazolium-based ionic liquids but in turn, the solubility of these ionic liquids into the CO_2 phase is negligibly small, thus greatly facilitating product separation and catalyst recovery.[11–13] Since then, the phase behavior of ionic liquids has been the subject of intense experimental[14–21] and theoretical investigation,[16,22–26] both exclusively focusing on imidazolium-based ionic liquids, except for one very recent report.[27] Here, we report the solubility of a phosphonium-based ionic liquid in dense CO_2 that we find to be surprisingly high, in sharp contrast to the solubility behavior of imidazolium-based ionic liquids. This finding could prove to be quite important for designing a single-phased ionic liquid–CO_2 solvent system. As pointed out previously,[28] such a single-phased ionic liquid–$scCO_2$ solvent system would be an intriguing medium for chemical synthesis because reactants of rather disparate polarity could conceivably be dissolved in one homogeneous phase, avoiding mass transport limitations through phase boundaries during the chemical reaction.

Experimental

The ionic liquid trihexyltetradecylphosphonium chloride (Cyphos® IL 101) was used as received from Cytec Canada. Water contamination in the ionic liquid was 0.2 mass%, as measured by means of Karl Fischer titration. The CO_2 gas was of 99.99% purity. Phase behavior was observed using a variable volume viewcell consisting of a modified manual syringe pump as described elsewhere.[29] The contents of the viewcell can be agitated with a magnetic stir bar. Temperature and pressure measurement precision were ± 0.5 °C and ± 0.1 bar, respectively.

The synthetic method for studying phase behavior was used. Known amounts of ionic liquid were inserted into the variable volume viewcell at ambient conditions and then CO_2 was added. The amount of CO_2 in the cell was determined from the initial (low) pressure and the known internal volume of the cell. Phase boundaries at a set temperature were visually observed as a disappearance of a phase boundary while incrementally decreasing volume, *i.e.* increasing pressure, as well as the reappearance of a phase boundary while incrementally increasing the volume, *i.e.* decreasing pressure. Both pressures are reported.

We observed discoloring of the viewcell contents when experiments were carried out for extensive periods of time at various temperatures up to 95 °C. Thus, to ensure that observed phase behavior was not compromised by any impurities, all reported measurements were carried out at temperatures below 70 °C. Furthermore, the viewcell was entirely disassembled and carefully cleaned after each series of measurements. The discharged ionic liquid from all reported measurements was colorless.

Fluorescence measurements were carried out on a Spex Fluorolog-3, with the ionic liquid, $scCO_2$, and the laser grade fluorophore coumarin-153 (C-153) contained in a stainless steel pressure cell with quartz windows. The contents of the high-pressure cell were homogenized using a magnetic stir bar and equilibrated. The temperature at which experiments were carried out was 50 $\pm$ 0.5 °C. Precision of recorded pressures was within ± 0.1 bar.

Results and discussion

While studying the solvation of ionic liquids in $scCO_2$ using fluorescence spectroscopy, which will be reported elsewhere in due course, we initially observed that the ionic liquid trihexyltetradecylphosphonium chloride dissolved to some extent in $scCO_2$. Fig. 1 shows an example of the excitation and emission spectrum of C-153 in $scCO_2$ with and without the

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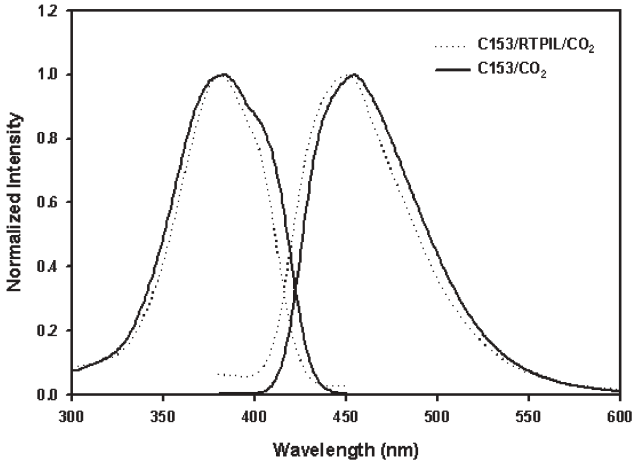

Fig. 1 Normalized excitation and emission spectra of C-153 in neat $scCO_2$ (solid line) and phosphonium ionic liquid–$scCO_2$ (dotted line). Data are shown for P = 104 bar and T = 50 °C.

presence of ionic liquid measured *in situ* at 50 °C and 104 bar. At this CO_2 pressure, the amount of ionic liquid in the cell is 3.5 mass%.

The ionic liquid–CO_2 spectra are very similar to the neat CO_2 data, but show two notable exceptions. First, the excitation data shows that the wavelength maximum is the same independent of the ionic liquid's presence. However, the spectral width narrows as ionic liquid is added. Conversely, the emission wavelength maximum is blue-shifted by approximately 9 nm upon addition of ionic liquid. Given the sensitivity of C-153 emission to its microenvironment we interpret this emission shift to clearly demonstrate that the ionic liquid was solubilized into the CO_2 phase. This initial observation prompted us to investigate the phase behavior of the phosphonium ionic liquid–CO_2 system in more detail.

Four isopleths are shown in Fig. 2 as P–T phase diagram contours at ionic liquid mass% compositions of m% = 2.49, 2.99, 5.79 and 6.50. At m% = 7 and higher the ionic liquid would not completely dissolve into the CO_2 phase, and small amounts of ionic liquid would still be visually present at the same pressure and temperature conditions shown in Fig. 2. Thus the solubility limit for the investigated conditions is believed to be m% = 7.

As is common in phase behavior studies some hysteresis behavior was observed for the appearance and disappearance of a two-phase boundary. Thus, Fig. 2 shows both the highest pressure recorded for observing two phases and the lowest pressure recorded for observing one phase. The true phase boundary should lie between these two pressure readings.

For comparison, the known vapor pressure curve of pure carbon dioxide (T_c = 304.13 K, P_c = 73.77 bar)[30] is also included in Fig. 2. Indeed, we observed for subcritical temperatures that the ionic liquid would completely dissolve as soon as all CO_2 condensed. Thus, the subcritical data points closely follow the vapor pressure curve of pure CO_2 with slightly higher pressures for the subcritical phase boundary data. From an application point of view, especially in terms of chemical synthesis, it is noteworthy that the ionic liquid is soluble in liquid CO_2 thus rendering high temperature and pressure unnecessary for obtaining a single-phased system.

The most striking feature of Fig. 2 is that within experimental uncertainty, the isopleths are of essentially identical shape. All four data sets can be fitted for the supercritical region to a second order polynomial

$$P(T) = -0.2107T^2 + 33.666T + 268.901 \quad (1)$$

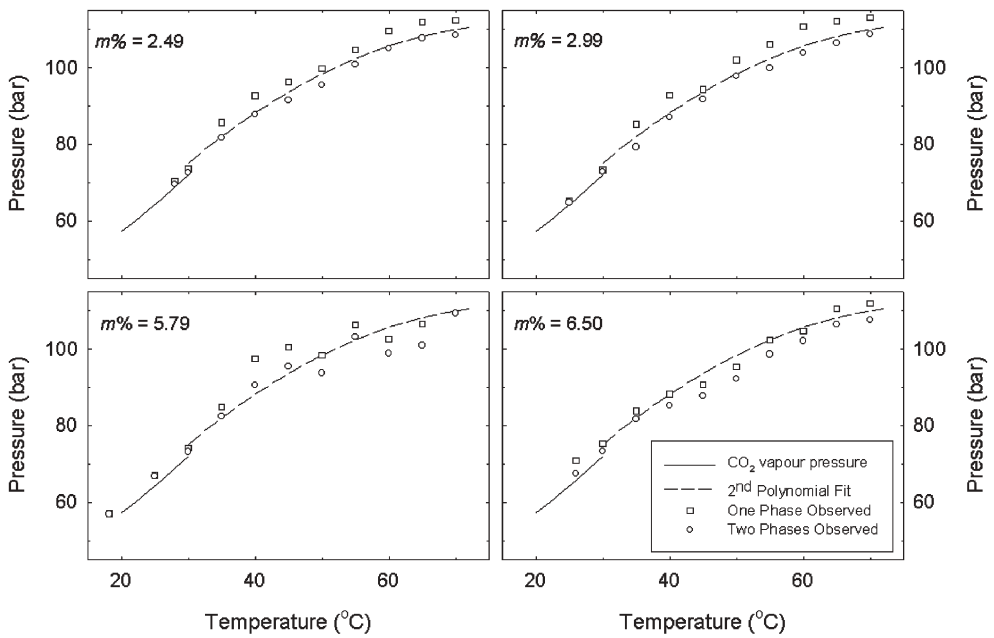

Fig. 2 Four P–T isopleth phase diagrams for m% = 2.49, 2.99, 5.79, and 6.50 of trihexyltetradecylphosphonium chloride in CO_2. Shown are the lowest measured pressures at which one phase was observed and the highest measured pressures at which two phases were observed. Within experimental uncertainty of the data the isopleths are essentially identical and can be fitted to a second order polynomial (dashed line). The vapor pressure curve of pure CO_2 is also shown.

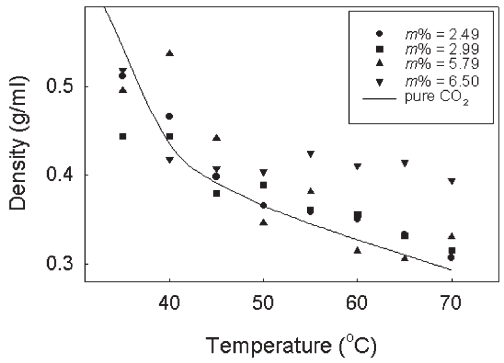

Fig. 3 Experimental CO_2 densities for the corresponding data points of the isopleths in Fig. 2. Except for the densities from the $m\%$ = 6.50 isopleth (above 50 °C) the density data points follow closely the density of pure CO_2 at same P–T conditions.

with an R^2 value of 0.99 to the averaged data points from the four isopleths in Fig. 2. Differently expressed, this finding means that an increase in pressure does not increase solubility at constant temperature. This type of phase behavior has also been observed for several other organic compounds in CO_2, albeit at higher pressures, for example above ~500 bar for adamantane, octacosane and squalane.[31]

Fig. 3 shows density data for the data points shown in Fig. 2 obtained from the measured volume displacements of the variable volume viewcell, neglecting the presumably small amounts of CO_2 absorbed into the ionic liquid at low pressures during loading.[14,27] The solid line shown in Fig. 3 is the density of pure CO_2 for the P–T conditions of the 2nd order polynomial fit to the isopleths in Fig. 2.[30] A significant local density augmentation of CO_2 around the dissolved ionic liquid should result in a positive deviation of the observed CO_2 densities compared to the densities of pure CO_2. Within the large measurement scatter, which is mainly due to the large uncertainty of volume displacement measurements for such a highly compressible system, the data overall follow the pure CO_2 density curve closely with a tentative exception for the $m\%$ = 6.50 isopleth above 50 °C where consistent positive deviations are observed.

Expressed in mole fractions, x, $m\%$ = 7 amounts to $x = 6.64 \times 10^{-3}$, or in other words one ionic liquid molecule in 150 CO_2 molecules, which is still fairly dilute in terms of number densities. Still, high molecular weight compounds such as surfactants and polymers usually only display comparable or higher solubility in CO_2, if they incorporate CO_2-philic functional groups in their molecular structure.[32–34] Compared to the solubility of imidazolium-based ionic liquids in CO_2, the mole fraction value of $x = 6.64 \times 10^{-3}$ is about four orders of magnitude higher.[35] It is interesting that alkanes of similar carbon numbers also display much lower solubility in $scCO_2$, by about 1–2 orders of magnitude with decreasing solubility as carbon number increases.[36] Thus, the much higher solubility in CO_2 compared to imidazolium-based ionic liquids cannot be attributed to the carbon side chains of the phosphonium cation alone.

We qualitatively tested the effect of the anion on the solubility of the phosphonium-based ionic liquid in CO_2. We observed that some but not all of the phosphonium ionic liquid dissolved into the CO_2 phase for the dicyanamide, the methane sulfonate bis(trifylfluoromethane-sulfonyl)amide, and the dodecylbenzenesulfonate anions, present at about $m\%$ = 5 in each separate measurement. We observed that in general dissolution of ionic liquid increased as the anion size decreased. It is well understood that charged or polar solutes solvate better in a high dielectric medium. The bulk dielectric constant of liquid or supercritical CO_2 has a rather low value of about 4.[37] The fact that the ionic liquid dissolves into the CO_2 phase at all is suggestive of ion pair formation. In fact, smaller anion size shifts the ion-pairing equilibrium towards contact-ion pairs as opposed to solvent-separated ion pairs.[38] Also, due to its relatively small size, the chloride anion is most capable of penetrating the bulky alkyl chains to be close to the positive charge bearing phosphonium center. It is conceivable that the ion-paired ionic liquid may be effectively viewed as one molecular unit bearing a dipole moment that interacts with the quadrupole moment of CO_2. This could serve as an explanation why the solubility of the studied ionic liquid is significantly larger than alkanes of similar carbon number. Structural *ab initio* calculations might prove to be very valuable in elucidating this matter but are beyond the scope of this report.

Conclusions

In stark contrast to the known phase behavior of imidazolium-based ionic liquids in CO_2, we reported unusually high solubilities of a phosphonium-based ionic liquid in CO_2. The observed solubility is also much higher than reported solubilities for alkanes of similar carbon numbers. This finding supports the idea that a single-phased mixed solvent system for chemical synthesis consisting of a suitably functionalized ionic liquid and $scCO_2$ is conceivable. For example, a phosphonium-based ionic liquid with perfluorinated alkyl chains is expected to be more soluble in $scCO_2$.[28] In this light, the recent findings of increased ionic liquid solubility in the presence of co-solvents are encouraging as well.[35,39–41]

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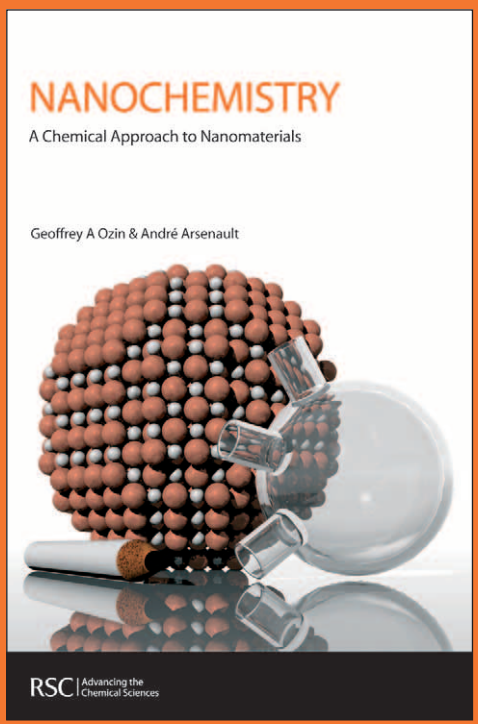

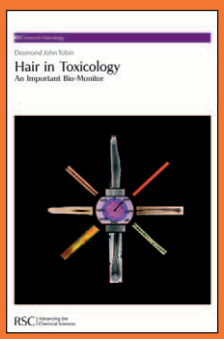

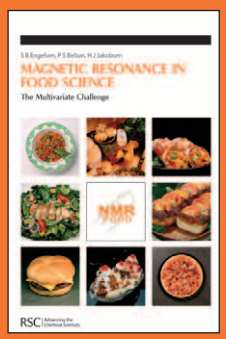

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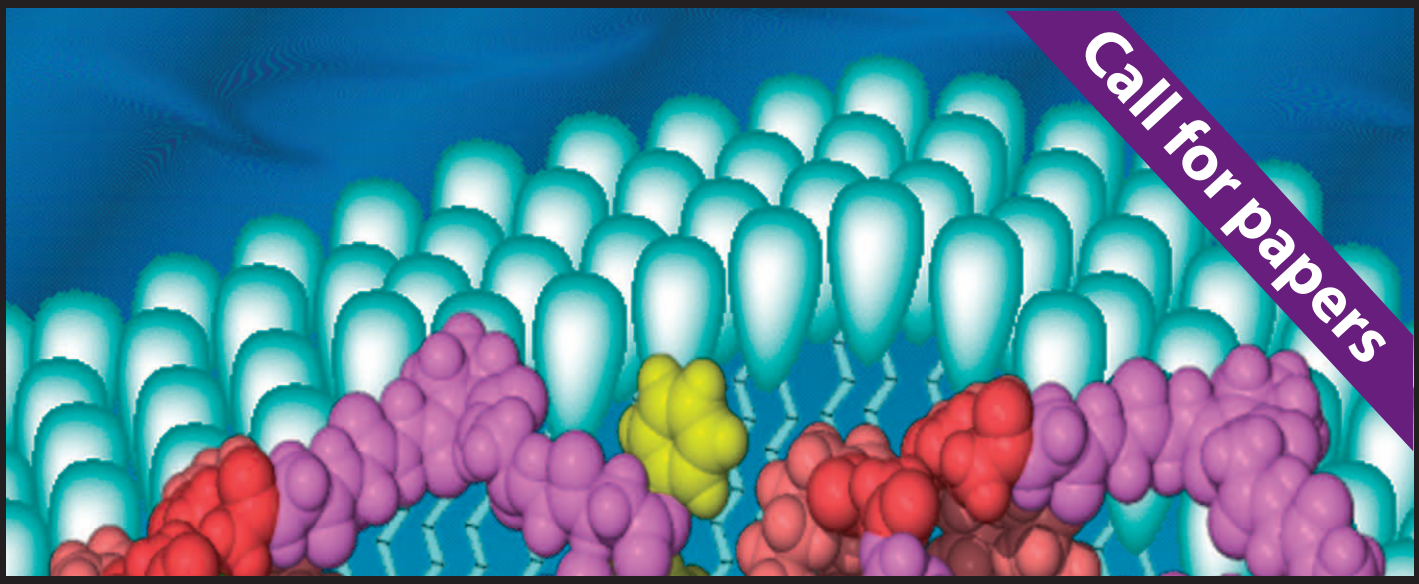

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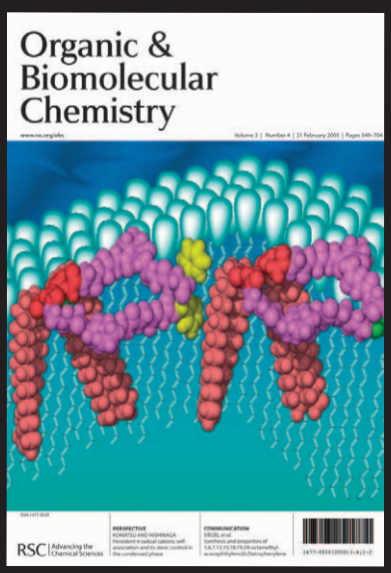

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