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Renewable energy and resources

Green chemistry can be considered as the design and application of processes and products that do no harm to the environment. With increasing demands for a higher standard of living from a growing world population, alternative feedstocks will be increasingly be needed to supplement traditional raw materials. Articles in previous issues of *Green Chemistry* have considered the potential value of crops as feedstocks for the chemical industry as well as their traditional use in foods. With modest improvements in farming efficiency it does seem as though we can see a future for chemical feedstocks beyond petroleum. In this issue of *Green Chemistry* we can read about two other very important aspects of renewable resources – biofuels and plans for a new European graduate course.

World demands for energy can be expected to grow significantly as developing countries seek to raise the standard of living of their citizens to those enjoyed elsewhere. This not only places an increasing strain on traditional energy sources, but also adds to the enormous global environmental and local health problems (as those who have recently visited many major cities in the western and developing countries will know). Funds based on biological resources such as biodiesels can help to alleviate these problems through extending the range of raw materials and through cleaner energy generation. The trend to utilise more renewable resource-based products in industry brings with it a need to translate the concept to education. The new European Masters programme on renewable resources is clearly a step in the right direction.

We recognise that there are a growing number of good examples of applications for non-traditional uses of biomaterials and of educational materials to demonstrate the importance of this emerging field. We hope to see more articles in these areas in future issues of *Green Chemistry*.

James Clark
York, July 2001

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2001 Green Chemistry Challenge Awards

The following are this year's recipients of the major US awards in green chemistry

Academic category

Professor Chao-Jun Li, Tulane University, was selected for designing a wide variety of transition metal mediated and catalyzed reactions that can be accomplished in air and water. Traditionally, these reactions have been carried out in an organic solvent under an inert atmosphere. Li has developed a novel [3 + 2] cycloaddition reaction to generate 5-membered carbocycles in water; a synthesis of beta-hydroxyl esters in water; a chemoselective allylation and pinacol coupling reaction mediated by manganese in water; and a novel alkylation of 1,3-dicarbonyl type compounds in water. In addition, a number of Barbier–Grignard type reactions in water have been developed. Water offers many advantages as a solvent. Water is readily available and inexpensive, and is not flammable, explosive, or toxic.

Protection/deprotection steps can be avoided, and products may be isolated by simple phase separation rather than by energy-intensive and organic-emitting processes involving distillation of organic solvent. Several reactions also demonstrate unprecedented chemoselectivity that eliminates byproduct formation and separation. The open-air feature offers convenience in operations of chemical synthesis involving small-scale combinatorial synthesis, large-scale manufacturing, and catalyst recycling. The catalytic reactions developed by Professor Li have widespread applications in the synthesis of pharmaceuticals, fine chemicals, petrochemicals, agricultural chemicals, polymers and plastics. Through his development of transition metal mediated and catalyzed reactions in air and water, Professor Li provides an attractive alternative to the inert atmosphere and organic solvents traditionally used in many synthetic reactions. *For more information on the work of Professor Li see http://www.tulane.edu/~ chemistry/ Li.html*

Small business category

EDEN Bioscience Corporation was selected for developing harpin technology that, when applied to crops, increases plant biomass, photosynthesis, nutrient uptake and root development, and ultimately leads to greater crop yield and quality. Harpins are nontoxic, naturally occurring proteins that trigger a plant's natural defence systems to protect against disease and pests and simultaneously activate certain plant growth systems without altering the plant's DNA. EDEN discovered that once a harpin protein binds to a receptor molecule on the plant surface, several biochemical events are induced. First, production of hydrogen peroxide, an important mechanism of plant defense, is induced in plant cells, followed by stimulation of a series of ion exchanges in the cell membrane. A series of signal transduction events leads to several beneficial plant responses. The result of this technology is an EPA-approved product called Messenger®, that has been demonstrated on more than 40 crops to effectively stimulate plants to defend themselves against a broad spectrum of viral, fungal, and bacterial diseases, including some for which there currently is no effective treatment. In addition, Messenger® has been shown through an extensive safety evaluation to have virtually no adverse effect on any of the organisms tested, including mammals, birds, honey bees, plants, fish, aquatic invertebrates and algae. In addition, harpin-based products are produced in a water-based fermentation system that uses no harsh solvents or reagents, requires only modest energy inputs, and generates no hazardous chemical wastes. As with most proteins, harpin is a fragile molecule that is degraded rapidly by UV and natural microorganisms and has no potential to bioaccumulate or to contaminate surface or groundwater resources. Using environmentally benign harpin protein technology, growers for the first time in the history of modern agriculture will be able to harness the innate defence and growth systems of crops to substantially enhance yields, improve crop quality, and reduce reliance on conventional agricultural chemicals. *For more information on Eden Biosciences and Messenger® see http://www.edenbio.com*

Alternative synthetic pathways

Bayer Corporation and Bayer AG were selected for their synthesis of a biodegradable chelating agent. Most classic chelating agents are poorly biodegradable; some are quite persistent and have been detected in the surface waters of rivers and lakes and in make-up water processed for drinking water. Bayer Corporation manufactures a readily biodegradable and environmentally friendly chelating agent, DL-aspartic-*N*-(1,2-dicarboxyethyl) tetrasodium salt, an aminocarboxylate also known as sodium iminodisuccinate. This agent is characterized by excellent chelation capabilities, especially for iron(III), copper(II), and calcium, and is both readily biodegradable and benign from a toxicological and ecotoxicological standpoint. It is also produced by a 100% waste-free and environmentally friendly manufacturing process. Nearly all aminocarboxylates in use today are acetic acid derivatives produced from amines, formaldehyde, sodium hydroxide, and hydrogen cyanide. The industrial use of thousands of tons of hydrogen cyanide is an extreme toxicity hazard. In contrast, Bayer's sodium iminodisuccinate is produced from maleic anhydride (a raw material also produced by Bayer), water, sodium hydroxide, and ammonia. The only solvent used in the production process is water, and the only side product formed, ammonia dissolved in water, is recycled back into sodium iminodisuccinate production or used in other Bayer processes. Because sodium iminodisuccinate is a readily biodegradable, non-toxic, and non-polluting alternative to other chelating agents, it can be used in a

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variety of applications that employ chelating agents, including detergents, agricultural nutrients, and household and industrial cleaners. *For more information see http://www.bayerus.com and http://www.bayer.de*

Alternative reaction conditions

Novozymes North America, Inc., was selected for designing an enzymatic process for treating cotton textiles that provides an economical and environmentally friendly alternative to alkaline scour systems currently used in the textile industry today. Conventional chemical preparation processes involve treatment of the cotton substrate with hot solutions of sodium hydroxide, chelating agents, and surface active agents, often followed by a neutralization step with acetic acid. This series of various treatments and rinsing steps generates large volumes of wastes, including large amounts of salts, acids, and alkali. The BioPreparation™ technology developed by Novozymes is an alternative to sodium hydroxide that offers many advantages for textile wet processing, including reduced BOD/COD, and decreased water use. Pectate lyase is the main scouring agent that degrades pectin to release the entangled waxes and other contaminants from the cotton surface. This enzyme is also compatible with other enzymatic preparations (amylases, cellulases) used to improve the performance properties of cotton fabrics. Because BioPreparation™ uses fewer chemicals and rinsing steps than required during a traditional caustic scour, textile mills may save as much as 30–50% in water costs by replacing caustic scours or by combining the usually separate scouring and dyeing steps into one. A recent statistical survey determined that 162 knitting mills used 89 million m^3 per year of water in processing goods from scouring to finishing; the BioPreparation™ approach would save from 27 to 45 million m^3 per year of water. In addition, field trials established that BOD and COD loads are decreased by 25 and 40%, respectively, when compared to conventional sodium hydroxide treatments. Furthermore, costs savings of 30% or more per mill can be realized. *For more information on Novozymes North America and BioPreparation® see http://www.novozymes.com*

Designing safer chemicals

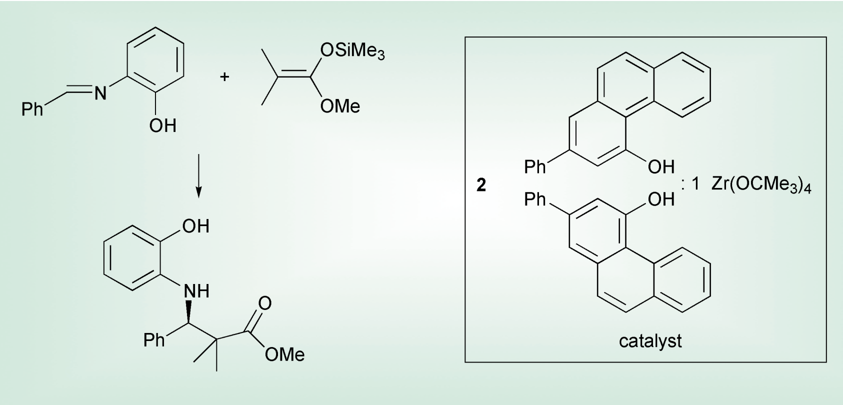
PPG Industries was selected for its discovery that yttrium can be used as a substitute for lead in cationic electrocoatings without any sacrifice in corrosion performance. Although much less studied that lead, the available data on yttrium indicate orders of magnitude lower hazard. As a dust hazard, yttrium is 100 times safer than lead at typical levels of use. In electrocoat applications, yttrium is twice as effective as lead on a weight basis, allowing the formulation of commercial coatings that contain half the yttrium by weight relative to lead in comparably performing lead-containing products. It has been found that yttrium is deposited as the hydroxide in an electrocoat, then converted to the oxide during normal baking of the electrocoat. The oxide is extraordinarily non-toxic by ingestion as indicated by the LD$_{50}$ of > 10 g kg^{-1} in rats, which is in stark contrast to lead. The ubiquitous nature of yttrium in the environment and the insoluble ceramic-like nature of the oxide combine to make it an unlikely cause of future environmental or health problems. An environmental side benefit of yttrium is its performance over low nickel and chrome-free metal pretreatments. By using yttrium in the electrocoat step, chrome can be completely eliminated using standard chrome-free rinses and low nickel or possibly nickel-free pretreatments, both of which are commercially available today. For PPG pretreatment customers, this should result in the elimination of up to 25,000 lb of chrome and 50,000 lb of nickel (annually) from PPG products. As PPG customers implement yttrium over the next several years, approximately one million lb of lead (as lead metal) will be removed from the electrocoat applications of PPG automotive customers. *For more information on PPG Industries and their electrocoatings see http://www.ppg.co*

Highlights

Duncan Macquarrie reviews the latest research in green chemistry

Imino-aldol reactions

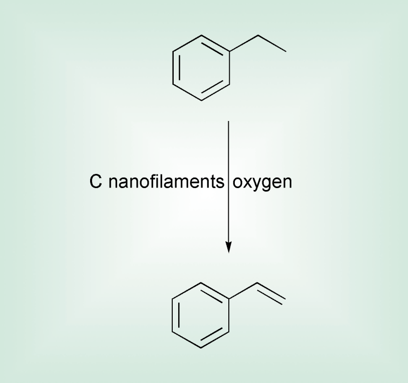
The imino-aldol reaction is a very useful method for the formation of amino acid derivatives. Obviously, enantioselective versions of this reaction are vitally important in the development of novel amino acids, and chiral amines. William Wulff and co-workers from Michigan State University, USA, have recently published work relating to two different ligand systems for the zirconium-catalysed reaction of imines with silyl acetals (*Angew. Chem., Int. Ed.*, 2001, **40**, 2271).



Their work involves the use of 6,6-dibromo-1,1':2,2'-binaphthyl (diBrBINOL) and the related VAPOL ligands, which form 2:1 complexes with Zr(O*t*Bu)$_4$. These complexes allow high levels of enantioselection to be obtained, with the VAPOL system yielding ee's of >98% even at 100 °C in some cases.

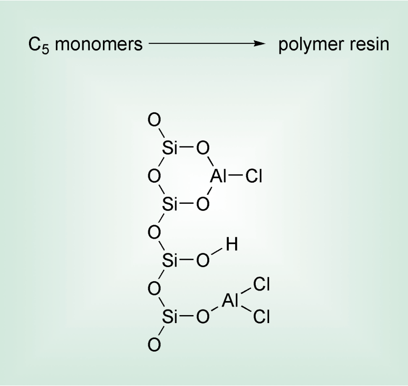
Ethylbenzene → styrene

One of the most important industrial processes is the oxidative dehydrogenation of ethylbenzene to styrene. Currently K-promoted iron catalysts are used in this process, which run at temperatures around 900 K. The process is thus energy intensive, and novel catalyst systems which can reduce the energy burden are welcome. Robert Schlögl and his group at the Max Planck Institute in Berlin, Germany, have published a new catalyst based on carbon nanofilaments, which allows the reaction to proceed efficiently at 830 K *(Angew. Chem., Int. Ed.*, 2001, **40**, 2066). Their initial idea came from the potential role of carbon deposits on various catalysts, and was developed by examining a series of carbons. They found that nanofilaments of carbon were both the most active and the most stable under the oxidative reaction conditions, something that precludes most carbon sources. Under their conditions, excellent activity could be sustained for several hours, indicating considerable promise for this new material.



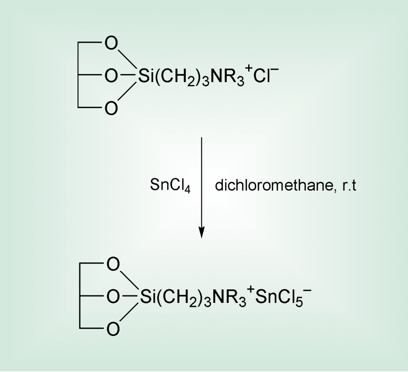
Polymerisation

The production of resins based on petrochemical feedstocks is a major area of polymerisation technology. James Clark and his group at York University, UK, have developed a heterogeneous AlCl$_3$-based catalyst system which is very effective at polymerising these monomer mixes, and avoids the need for an aqueous quench reaction to remove the catalyst (*Org. Proc. Res. Dev.*, 2001, **5,** 249). Their catalyst is also very effective at increasing polymer yield and importantly, controlling the molecular weight distribution, critical to the successful application of the polymer.



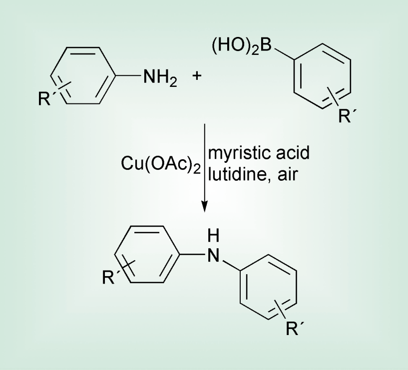
Immobilised Lewis acids

An interesting route to immobilised Lewis acids has been published by the group of M. V. Landau at the Ben Gurion University in Beer-Sheva, Israel (*Chem. Commun*., 2001, 992). Their approach utilises quaternary ammonium species immobilised on mesoporous high surface area silicas. These are present in the form of chlorides, and it is the chloride which behaves as a Lewis base to complex the acidic component. They have shown that quaternary supported tin tetrachloride is active in the Prins condensation of formaldehyde and isobutene to isoprenol. Interestingly, it is significantly more active than the same Lewis acid directly adsorbed on the silica support. This may provide a useful general method for the immobilisation of Lewis acid, complementary to the direct attachment route.



Arylamines and diarylamines

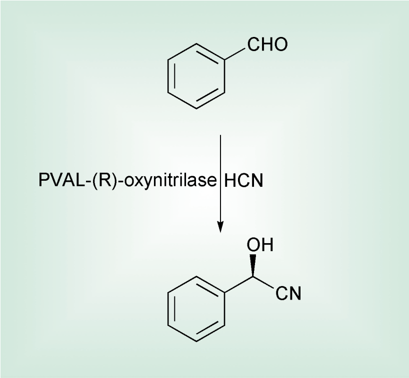
The synthesis of arylmines and diarylamines is required for the synthesis of many bioactive compounds, as well as antioxidants (see *Green Chem*., 1999, **1**, G41 for an alternative clean synthesis of a diarylamine). Jon Antilla and Stephen Buchwald at Massachusetts Institute of Technology (MIT), USA, have now developed a method for the coupling of amines with arylboronic acids, which relies on a copper acetate catalyst (*Org. Lett.*, 2001, **3**, 2077). This reaction proceeds under air, which appears to be vital for the re-oxidation of the copper, and myristic acid, which helps to solubilise the catalyst system. Even under non-optimal conditions for oxygen transport, the reaction proceeds very well, giving high yields of product. Functional group tolerance is excellent, and appears to be better than with Pd-based couplings, with amides and alcohols reacting smoothly. Aliphatic amines also give reasonable results.



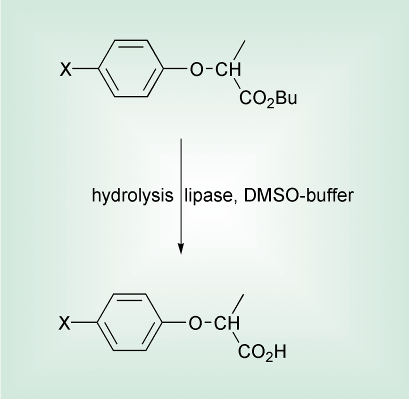
Enzymes

Immobilised enzymes represent an interesting class of asymmetric catalysts, combining the advantages of an efficient reaction under mild conditions with the ease of separation of heterogeneous catalysts (in optimally designed systems). The group led by Harald Gröger at Degussa and the Institut für Technoligie und Biosystemtechnik in Braunschweig, Germany, have published details of such a system, consisting of (*R*)-oxynitrilase entrapped in a poly(vinyl alcohol) matrix (*Org. Lett.*, 2001, **3**, 1969). They have found that this immobilised enzyme can catalyse the addition of HCN to benzaldehyde in excellent yield and ee to give (*R*)-mandelonitrile at room temperature and slightly acidic pH. Yields in the best solvent system were higher than with free enzyme, and ee's were always above 90%, some as high as 99%. Leaching was not found, and the catalyst could be recovered and recycled.

A further interesting paper on enzyme-catalysed reactions comes from

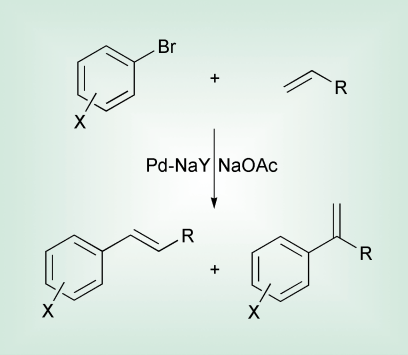


Keichi Watanabe and Shin-ichi Ueji from Kobe University, Japan (*J. Chem. Soc., Perkin Trans. 1*, 2001, 1386). They have found that the simple addition of around 50% DMSO to the aqueous buffer system has an enormous positive effect on the enantioselectivity. For example, the lipase-catalysed hydrolysis of various phenoxypropionates gives an enantiomeric excess of 25–49%, depending on the structures, when no DMSO is present. Addition of DMSO to the reaction medium causes the ee to rise to 100%, at the cost of a slower reaction (*ca.* 5–6 times longer reaction time). Various lipases gave similar effects.



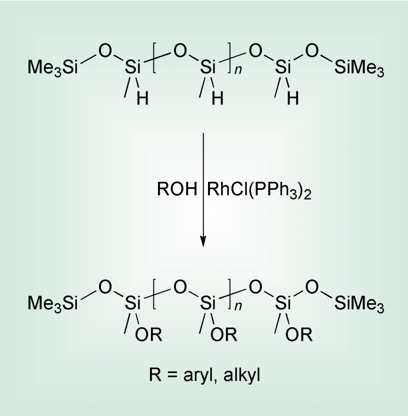
Heck reactions

Heterogeneous Heck catalysts continue to be of interest. Laurent Djakovitch and Klaus Koehler of the Technishce Universität in Munich, Germany, have now described a Pd–NaY zeolite catalyst which shows excellent activity in the coupling of aryl halides with alkenes (*J. Am. Chem. Soc.*, 2001, **123**, 5990). They exchanged Na–Y zeolites with Pd species and then used them in the Heck reaction of a series of reaction partners. Their results indicated that the catalyst was highly active, converting activated substrates rapidly and in high yields, and even showing some activity for aryl chlorides. The catalysts could be recovered and reused with almost identical activity. No leached Pd could be detected.



Functionalisation of silicones

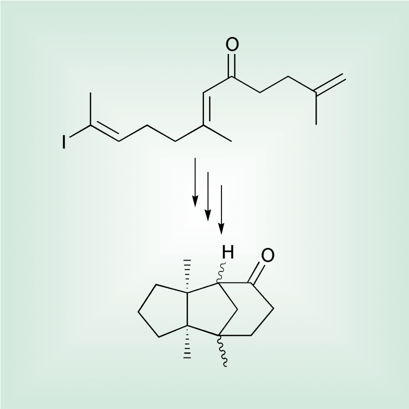
Functional silicones are interesting materials for a wide range of applications, including advanced electronic and optical devices. However, the functionalisation of simple polysiloxanes, carried out by oxidative addition of the Si–H groups on the backbone to alcohol groups, is plagued by problems of selectivity—several side-products are formed, and control over the exact nature of the product is difficult. Philip Boudjouk and his group at the Center for Main Group Chemistry at North Dakota State University, USA, have now provided an effective Rh catalysed route to these important materials (*Organometallics*, 2001, **20**, 2725). They used $RhCl(PPh_3)_2$ to effect the alcoholysis of the Si–H bond with a range of alcohols, leading to high levels of functionalisation, without the problems of crosslinking and isomerisation generally seen with existing systems. Many different functionalities can be introduced, making the method versatile. The only solvent used in the paper was d_6-benzene, as the reactions were all monitored *in situ* by NMR, but it seems likely that other solvents could easily replace benzene in a more practical system.



R = aryl, alkyl

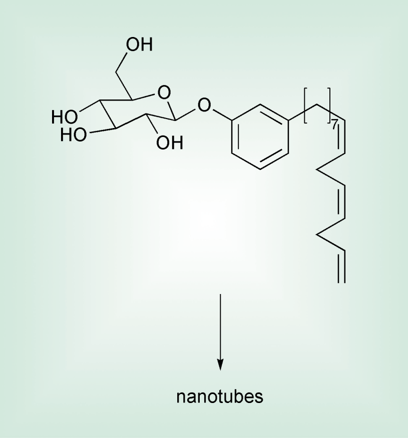
Cascade reactions

Cascade reactions are making a significant impact in organic synthesis, due to their advantages of minimising the number of isolation stages that have to be carried out, simplifying multi-step synthetic strategies, and eliminating wasteful purification of intermediates. Andrew McCorrel and John Walton of St Andrews University, UK, have published an excellent review on radical cascade processes (*Angew. Chem., Int. Ed.*, 2001, **40**, 2224) in which they discuss a wide range of radical based one-pot multistep synthetic methods, many of which have potential for minimising environmental impact.



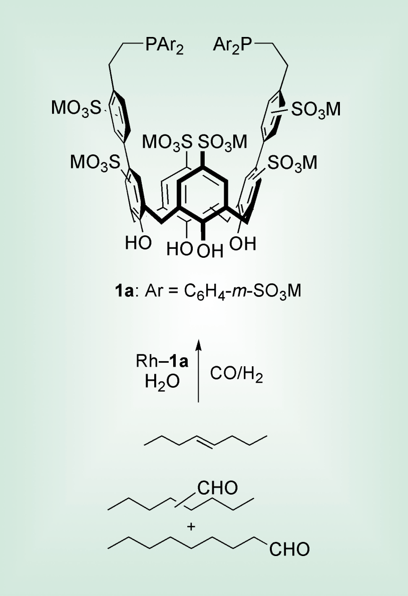
Supramolecular assemblies

Supramolecular assemblies with defined architecture are proving to be very versatile and popular in the field of new materials and nanotechnology. While the vast majority of the materials prepared are derived from petroleum-based feedstocks, relatively little has been done in the field of renewable raw materials in this are. The group led by George John and Toshimi Shimizu of the CREST of Japanese Science and Technology and the AIST in Ibaraki, Japan, has now published a route to nanotubes based on cardanol, a product derived from cashew nuts (*Adv. Mater.*, 2001, **13**, 715). A mixture of four glycosides (the one shown and the corrsponding diene, monoene and saturated equivalents, saturation beginning from the terminal double bond and progressing towards the aryl group) were dissolved in hot water and allowed to cool. This produced supramolecular assemblies, with the pure saturated glycoside giving nanotubes. Such nanotubes could have a range of applications in catalysis, electronics and separation technology amongst others.



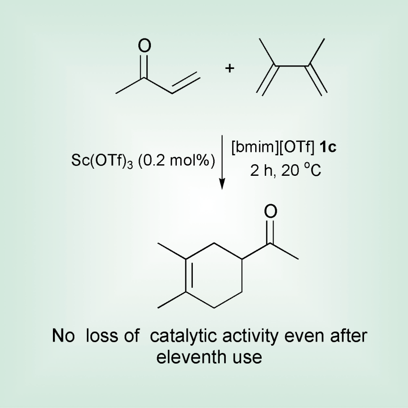
Alkene hydroformylation

Hydroformylation of alkenes is a key process for the functionalisation of alkenes. Biphasic systems with water soluble metal complexes have shown promise, but have some drawbacks, especially in the case of internal alkenes. Progress in this respect has recently been described by Shoichi Shimizu and co-workers from Nihon University in Chiba, Japan (*New J. Chem.*, 2001, **25**, 777). They used a calixarene-based ligand system for a rhodium complex as a water-soluble catalyst, and found that excellent conversions could be attained over several cycles, overcoming the drawbacks seen with other methods. Isomerisation of the alkene double bond leads to all four possible aldehydes from *trans*-4-octene, although the quantity of the most desirable product, the terminal aldehyde does not exceed 24%; work is ongoing to improve this.



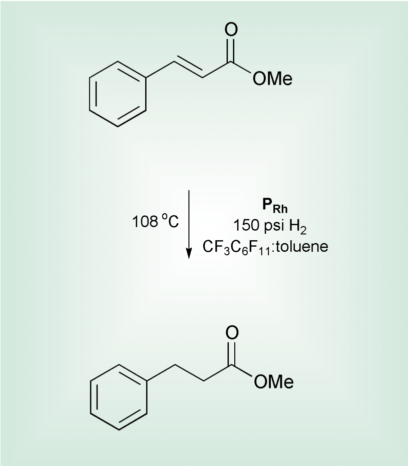
Diels–Alder reactions

The combination of ionic liquids and scandium salts has been found to be a very powerful method for the Diels–Alder reaction. Choong Eui Song, Jung Hoon Choi and their groups at Korea Institute of Science and Technology and Hangyang University, Seoul, South Korea, have found that the use of scandium triflate in very small amounts in ionic liquids allows the Diels–Alder reaction to be performed much more rapidly than in many organic solvents, with quantitative yields (*Chem. Commun*, 2001, 1122). The *endo* : *exo* ratio is also excellent at 99 : 1. An additional bonus is that the catalyst can be recovered easily and reused several times by simple phase separation. No loss in activity or yield was noted after 11 cycles.



Fluorous biphase catalysts

Fluorous biphase catalysis is another innovative way to effect reactions and utilise phase behaviour to isolate reaction components, this time by the temperature-dependent miscibility of certain perfluorinated solvents and hydrocarbon solvents. One of the difficulties associated with this technique is the need to functionalise catalysts with fluorous 'pony-tails' to solubilise them in the reaction medium, which is typically much less polar than even a hydrocarbon. Shannon Vinson and Michel Gagné of the University on North Carolina, USA, have now demonstrated that a polymer-supported hydrogenation catalyst (based on a Rh-diphosphine copolymerised with ethylene glycol dimethacrylate) works extremely well under fluorous biphasic conditions (*Chem. Commun*., 2001, 1130). They found that hydrogenation of methyl cinnamate was complete 2–3 times faster than in conventional solvent systems. Surprisingly, they also observed that reaction rates increased with increasing perfluoro content of the solvent mixture. While separation of a heterogeneous catalyst does not require a biphasic solvent system, the observation that there may be potential benefits of using fluorous solvent systems (and possibly much more so for oxygen- based oxidations) is an important observation.



European teaching on renewable resources

In the framework of a European Curriculum Development Programme, a group of European universities are collaborating in order to create a European masters programme on renewable resources. The CDA (Curriculum Development Advanced) programme aims at starting the master studies in 2004, if approved by the EU at that time

In response to the trend to promote and utilise more renewable resources based products in industry, the need to translate this trend in education became urgent. Further, the need to train people in an European environment in order to prepare them for the challenges of global thinking and acting, supported the idea to create a think tank for the organisation of a European masters programme. Several European universities active in the domain of renewable resources became involved in the CDA programme and are developing a practical system for the masters programme. Among the universities involved are:

- Akademia Rolnizca (Wroclaw, Poland)
- Institut National Polytechnique de Toulouse (Toulouse, France)
- Joensuun Yliopisto (Joensuu, Finland)
- Justus-Liebig-Universität Giessen (Giessen, Germany)
- Kauno Technologijos Universitetas (Kaunas, Lithuania)
- Sveriges Lantbruksuniversitet (Uppsala, Sweden)
- Universität für Bodenkultur Wien (Vienna, Austria)
- University of York (York, UK)
- Westfälische Wilhelms-Universität Münster (Münster, Germany) and
- Ghent University (coordinator, Ghent, Belgium).

The aim of the programme is to educate young academics with the ideas of the use of renewable resources, sustainable development and green chemistry. Within the programme, special attention will be paid to topics related to:

- European policy and socio-economical aspects of the use of renewable resources
- the production of renewable resources
- downstream processing
- non-food applications of saccharides, proteins, oils and fats
- renewable energy
- green chemistry
- wood and fibres
- high-value added materials *etc.*

On top of the technical and technological aspects of the programme the students will benefit from the international environment and the experience offered by the master programme since the courses of this two-year programme are planned to be given in a modular system in at least three (or four) different universities. This means that students will need to move to different countries, thus accumulating major cultural, lingual and international experience which will be of major importance for a job career in a unified European market.

The cost of the master programme is planned to be supported strongly by the European Community and the student and staff mobility programmes of the EU. In this way students will be in touch with European experts of the different topics included in the programme. Within the programme, much attention will also be paid to practical work and case studies, as well as to a research period in a university of choice within the programme. Flexibility and tailor made programmes for students with a certain background will be a major concern of the organisation. Therefore, the programme will be suitable for agricultural engineers, chemists, foresters, biochemists, bio-engineers *etc.* In view of the development of the educational system within Europe, the programme might become a preferred education option in a 3 + 2 education system as proposed in the Bologna and Prague declarations of the EU.

Universities and institutes interested in the further development and organisation of this master programme on renewable resources may contact: Prof. Dr. ir. Christian Stevens, Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure links 653, B-9000 Gent, Belgium, e-mail: Chris.Stevens@rug.ac.be; Fax : 0032 (0)9 264 62 43.

Towards a metabolic society: a thermodynamic view

Jakob de Swaan Arons and Hedzer J. van der Kooi of the Laboratory of Applied Thermodynamics and Phase Equilibria, at Delft University of Technology in The Netherlands[†] present a thermodynamic argument that our society should develop to become a metabolic society,[1,2] involving more efficient conversion and disposal of energy and material. Most living systems fulfill the requirements of a metabolic society, directly (plants) or indirectly (animals).[3] The notorious exception is man as from the moment that he got involved in what is called the industrial society'. How can this unfortunate exception be repaired?

Introduction

The 20th century showed the full development of an industrial society characterized by mass production, mass consumption and mass waste disposal.[1] For many countries this has produced prosperity and an unprecedented economic growth with, in many respects, an improved quality of life. But gradually less attractive consequences of this development became apparent, like the dependency on fossil fuels and the impact on the environment that seem to have taken global proportions. So on the way to the 21st century we began to realize that this posed us for a Trilemma, where we are challenged to devise a way to harmonize economic growth, resource supply and preservation of the environment.[4]

Prominent representatives of industry, government and academia, recognizing this Trilemma, therefore have called for 'sustainable development', often with a less precise description albeit with the best of intentions. Sawa for example proposes that the 21st century should see the development of a post-industrial society, *the metabolic society*, characterized by viable consumption levels, limited waste, active recycling, energy savings and longer product lives.[1] This is a very interesting proposal and we felt the need to try and identify the characteristics of such a society. Therefore we have turned to living systems and identified some of their basic requirements with regard to the conversion of energy and matter.[3] Next we tried to analyze the way we 'manage our house' by starting from a simple economic picture and by extending it to what we believe is a picture of a self-sustaining, rather than of a self-exhausting society. Finally we present a perspective of the global industrial society from how it is to how it should develop.

The metabolic society

When Sawa launched the term 'metabolic society' he may have had in mind a society that lives in dynamic equilibrium with its environment, producing enough food and materials to sustain its passive and active life and absorbing in a natural way all its waste produced, like a cow living on a pasture of sufficient area, the total system powered by the sun. This is what many believe to be a sustainable society. Angela Merkel, physicist and former German Minister of the Environment defines sustainable development as 'Using resources no faster than they can regenerate themselves and releasing pollutants to no greater extent than natural resources can assimilate them'.[5] This was of course the situation before the industrial revolution and man fitted quite nicely in such a society. But then he got engaged in the industrial society, and by doing so stepped out of the metabolic society. A point was reached that 'nature could not keep up with us any longer', as Yoda puts it.[4]

Morowitz has summarized some characteristics of living systems.[3] They prevail in a permanent non-equilibrium with respect to their environment. This state is sustained by a permanent energy source. They display structure and prevail in an active or passive mode. The energy source needs a sink for disposal of its degraded form, while stripping energy from its useful part requires at least one material cycle. Fig. 1 shows schematically the metabolic society. Radiation from the sun is stripped from its useful component and transformed into mechanical, electrical or chemical energy. Overall, solar radiation is converted into the same amount of useless heat to the environment while sustaining a structured, non-equilibrium system of plants and animals, requiring at least one material cycle of synthesis and respiration involving CO_2, H_2O and O_2. In this cycle the smallest living systems, the microbes, are most numerous and essential. They keep matter in cycles and are also responsible for the final degradation step to CO_2 and H_2O, thus assuring 'waste' disposal.

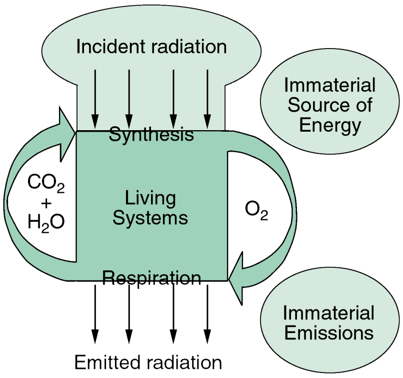


Fig. 1. The metabolic society.

The industrial society

Ecology is the study and economy in the management of 'the house'. So let us see how we manage the house in which we live, the industrial society. Fig. 2 and Fig. 3a picture the classical way of thinking in

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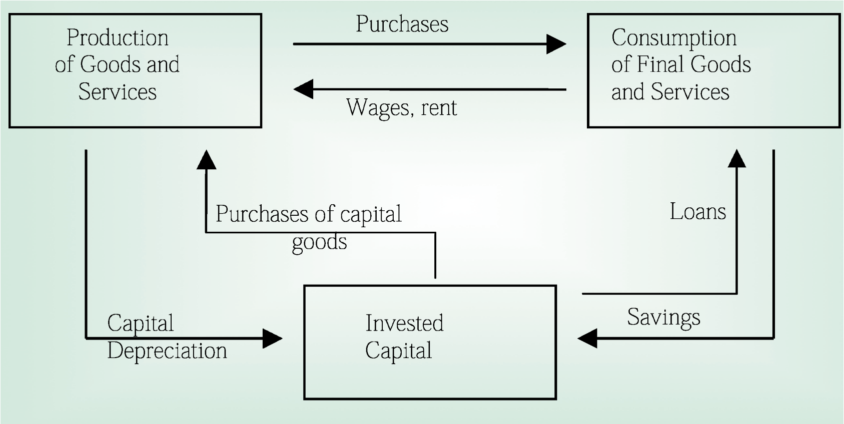

Fig. 2. Classical economics.

economics in which capital, production and consumption stand out. However environmental economists pointed to what is missing in this picture: the environment. In thermodynamics we know all too well that we should always look at the system *and* its environment. Aware of this, environmental economists emphasize the importance of the interaction with the environment *via* extraction and emission (Fig. 3b). This picture expresses somehow the less favourable aspects of an industrial society. Ishikawa condemns this by stating that ‘we contaminate the environment by squandering natural resources’.[6] In this respect the industrial society is markedly different from the metabolic society and much more primitive. At one time man stepped out of nature's cycles. We may now have reached a state in which we are called back to order. Fig. 3 also allows us to point to what it takes to make the transition back from industrial to metabolic.

We realized that Fig. 3b can be further extended by closing the cycle between emissions and extraction. The amount of work that this requires necessarily has to be paid for by a renewable source of work, Fig. 3c. Otherwise other non-closed cycles would be introduced. This picture helped us to arrive at a possible thermodynamic definition of sustainability:

- close all product cycles
- drive all cycles with renewable energy
- do it efficiently

Thermodynamic parameters can now be defined[7] to calculate and measure to what extent a society is sustainable. It may not make sense to make use of renewable energy while this is done inefficiently, nor might it suffice to use renewable energy efficiently when material cycles are not closed. By the way, an interesting consequence of this analysis is that the generating cost of a fossil fuel must always be higher than that of a corresponding amount of a renewable energy source.

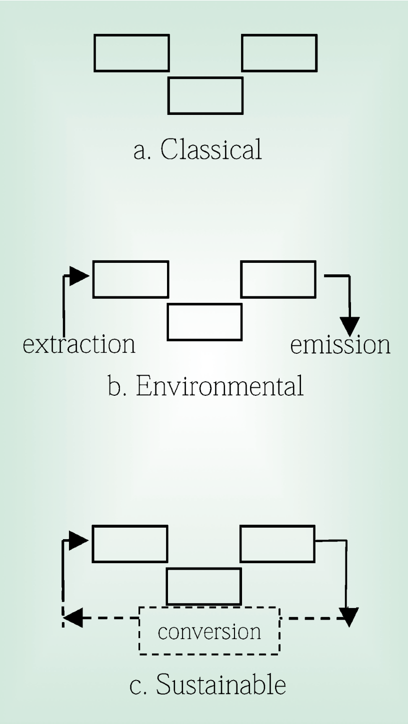

Fig. 3. Extension of classical economics.

Thermodynamic perspective

Thermodynamics has provided us with two very useful concepts, both originating in the two fundamental laws: *available work* and *lost work*.[8] Both concepts can be calculated and easily communicated to non-experts as we hope to demonstrate.

Fig. 4 pictures the fate of work, as available in ‘methane’ (natural gas), in the chain from gas production to utilization. The picture clearly shows the transformations that take place in time and allows some important observations. First and foremost it visualizes the first and second law. Although energy is conserved, its quality, *i.e.* its available work content, diminishes and finally disappears while the amount of lost work increases in time. Secondly it makes us aware that a material resource of energy has depleted and that its transformation is accompanied by emissions due to the law of mass conservation: mass stored underground and mass extracted from the atmosphere are transformed and sent into the atmosphere. Thirdly the application, electricity consumption, does not need a material source of energy. An immaterial source of energy as solar radiation can also provide electricity. Finally, if we make a life cycle analysis of this process, we notice that the process is not a closed cycle.

Fig. 5 tries to picture that the work originally *available* in fossil fuel is used to pay for global energy needs, is lost in

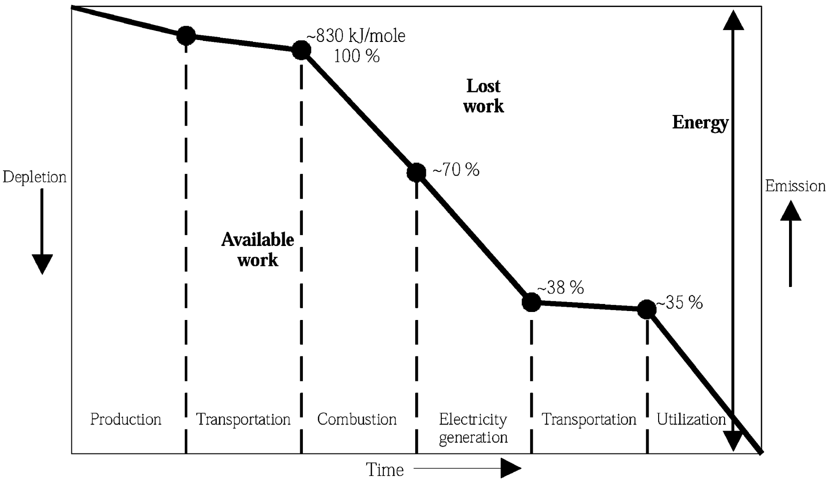

Fig. 4. The fate of work from natural gas.

Fig. 5. The fate of fossil fuels.

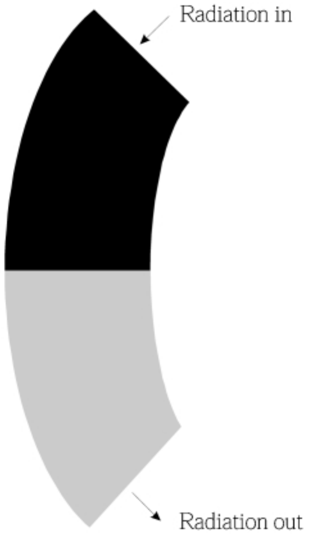

Fig. 6. The fate of incident solar radiation.

time and that the mass in which this work was stored is conserved and emitted. The overall conclusion is that as most (> 90%) of the fossil fuel is used for 'energy' purposes, *i.e.* not requiring a material resource for the work required, a massive flow of matter is generated, unnecessarily.

At the same time we should realize that the work available in the incident solar radiation is orders of magnitude greater than what the world in its human activities transforms into lost work.[2] The fate of this available work however is the same as that in most of the consumed fossil fuel: lost work. The work is dissipated and although the radiation from the earth is still valuable for bodies at a lower temperature than the earth, it has lost its power for the benefit of the earth (Fig. 6).

The challenge is now to tap the work available in the incident radiation and thereby to eliminate largely the massive material emissions associated with the consumption of fossil fuel: the dematerialization of energy sources. Fig. 7 tries to picture this. In contrast to Fig. 5 the required work is now available in an immaterial resource and consequently no net flow of matter is associated with it: 'the solar fueled globe' where the dissipation of the work available in solar radiation (Fig. 6), is now delayed for the benefit of the globe's industrial activities.

Fig. 7. A solar fueled globe.

However, here is a point of concern. There is strong evidence[2] that the globe's ecological capacity is no longer sufficient to fulfill our energy needs by photosynthesis. This then asks for alternative extraction of the work available in solar radiation and, possibly, for a further reduction in human material needs.

Conclusion

In comparing characteristics of a metabolic society with those of an industrial society one cannot help but conclude that the latter is far more primitive in terms of access to, and conversion and disposal of energy and matter. Man can learn much from the study of natural processes and may have to conclude that he should become part again of natural cycles much as he did before the industrial revolution. This may imply a simultaneous reduction of his material needs.

Acknowledgement

We express our appreciation to economists/physicists Professor Robert Ayres (INSEAD, France) and Dr. Stefan Baumgärtner (University of Heidelberg, Germany) for all we learned from them at the Gordon Research Conference on Thermodynamics, Pisa, Italy, April 1999.

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A greener future with biodiesel

Jeffrey Hardy, a Green Chemistry Teaching Associate at the Clean Technology Centre at the University of York, UK, describes the sources and production of this renewable transport fuel, and argues the case for its wider acceptance

Introduction

Biodiesel is a renewable transport fuel made mainly from vegetable oils. It is not a new fuel; in fact Rudolf Diesel ran his original engine on peanut oil in 1900. The reason why people are not familiar with biodiesel is that because mineral oil derived diesel has been cheaper and more available for the majority of this century. The oil crisis in 1973 reawakened interest in biofuels when mineral oil prices skyrocketed. Now, even though the oil prices have fallen again the interest in biofuels has not diminished due to the environmental advantages of biodiesel.

Biodiesel is quite simply a fuel made from vegetable oil. More precisely it is defined as the mono alkyl esters of long chain fatty acids derived from renewable lipid sources. The processing required to produce biodiesel is minimal, firstly oil has to be extracted from the crop and secondly a very simple chemical modification of the oil has to be carried out. Biodiesel can be used in an unmodified diesel engine as either pure biodiesel or as a mixture of biodiesel and conventional mineral oil based diesel. A tractor fuelled by biodiesel derived from sunflower oil has been successfully driven from Lands End to John o' Groats (Fig. 1).

The source of oil for biodiesel production depends on the agriculture of the country where it is produced. For instance in Europe it is produced from oilseed rape and sunflower oil, in North America from soya oil and in South East Asia from palm oil.

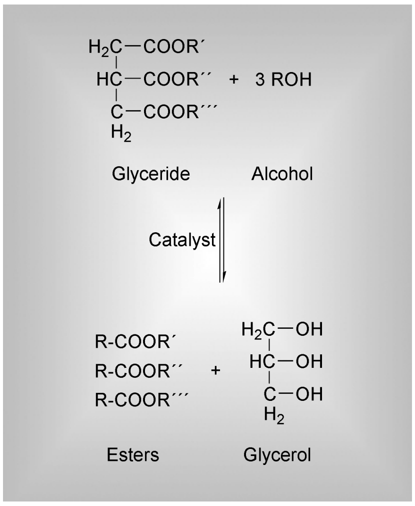
There are several key advantages biodiesel possesses over conventional diesel. Perhaps first and foremost is the fact that biodiesel is neutral with regard to carbon dioxide (CO_2) emissions and consequently it does not add to global warming. This is in stark contrast to conventional diesel, which produces three tonnes of CO_2 for every tonne of diesel burnt. Biodiesel is also non-toxic (less toxic than table salt according to the EPA) and degrades quickly in the environment leaving innocuous products. Unlike mineral oil diesel, biodiesel has a negligible sulfur content and consequently it does not add to acid rain. Biodiesel is a much better lubricant than conventional diesel fuel and extends engine life—a German truck won an entry in the Guinness Book of Records by travelling more than 1.25 million km (780,000 miles) on biodiesel with its original engine.[2] Biodiesel is also the only alternative fuel to have passed the stringent health effects testing requirements of the US Clean Air Acts Amendments of 1990.[3]

Methods of producing biodiese

Vegetable oils can be used directly as diesel fuels, but the inherent viscosity of the oils is often a problem. This can be solved by the formation of micro-emulsions with solvents such as methanol and ethanol. However, neat vegetable oils and the emulsions both cause coking and valve blocking in engines due to problems deriving from oil deterioration and incomplete combustion.

Fig. 1. Tractor fuelled by biodiesel.[1]

The most widespread method for production of biodiesel is through a transesterification process. Natural fats and oils exist as glycerides, a triester of fatty acid and glycerol, which are naturally viscous by nature. The transesterification process involves the reaction of a fat or oil with an alcohol to form esters and glycerol (both of which are commercially saleable products).[4] A general reaction is shown below in Scheme 1.[5]



Scheme 1. Transesterification of triglycerides with alcohol.

A catalyst is generally used to improve the reaction rate and yield. Because the reaction is reversible, excess alcohol is used to shift the equilibrium to the product side (the alcohol is recycled). Methanol is the most commonly used alcohol because of its low cost and physical and chemical advantages (polar, shortest chain alcohol and sodium hydroxide, a basic catalyst, is soluble in it).

The ratio of alcohol to glyceride required for reaction is dependent on whether the reaction is catalysed by acid or base. An acid catalysed reaction needs a ratio of 30 : 1, whereas a base catalysed reaction (*ca.* 1% w/w for both acid and base) requires a ratio of 6:1. A major point is that the base catalysed system is intolerant to water content in the vegetable oil, whereas acid catalysis can tolerate water. Enzyme catalysts have also been used.[6]

A typical continuous reactor used in the production of biodiesel from various sources is shown below in Fig. 2. The oil is added separately to the alcohol and catalyst. The reagents are passed through a heated column where reaction takes place. The esters are then separated from glycerine by gravity.

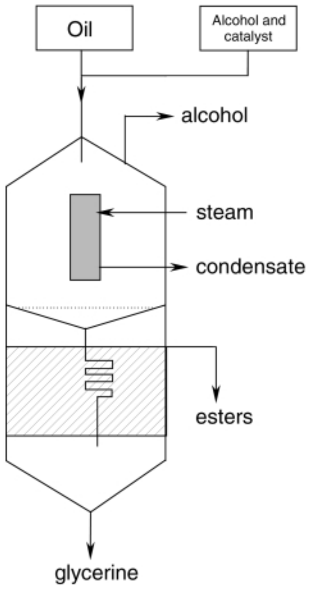


***Fig. 2.** A continuous transesterification reactor.*[7]

UK case study

Although significant progress regarding the introduction of biodiesel has been made in several European countries in the UK there still remain several hurdles to overcome. The major obstacles are clearly outlined by examining the case of Martin Steele.[10,11] Using his ingenuity Mr. Steele has developed a transesterification process to turn used chip pan fat into perfectly functional biodiesel. In fact he has successfully run his Volvo car on his biodiesel fuel (produced in his Manchester back garden) for over 18,000 miles. The car engine was examined after 15,000 miles and was found to be virtually corrosion and carbon deposit free. This proves the validity of the fuel, and at a small scale production cost of 12p per litre it would appear to be competitive with regular diesel. The major problem arises when Customs and Excise demand he pays around 50p per litre in road fuel tax. Mr. Steele comments on this by saying ‘The Government talks about saving the environment and cutting down on emissions, but taxes biodiesel at the highest rate in the world. It’s daft!’ He also claims that the problem arises from a ‘wrong calculation’ by MAFF in a report to the government back in 1996 ‘One wrong figure in the report has set biodiesel production in the UK back by 5 years’. Furthermore, Mr. Steele attacks the UK Government on the subject of road tax ‘The Chancellor last year took £55 off road tax on small cars with no measurable benefit in terms of greenhouse gas savings. That cost the Exchequer £110 million. For the same amount of cash, we could have a brand new biodiesel industry in the UK, creating 2000 new jobs. It would have supported the production of 500 million litres of biodiesel, saving in round terms, half a million tonnes of carbon emissions’.

Mr. Steele continues his campaign to have the duty on biodiesel reduced. He is also involved in trying to set a larger scale production plant in collaboration with other biodiesel enthusiasts.

Other countries producing biodiesel

Biodiesel is seen as an important tool for the EU to meet its emission reduction target (Kyoto agreement). Specific legislation to promote and regulate the use of biodiesel is in force in various countries (including Austria, France, Germany, Italy and Sweden). Europe currently produces 700,000 tonnes/year of biodiesel and has set production targets of 2.3 Mtonnes by 2003 and 8.3 Mtonnes by 2010 to reduce greenhouse and air polluting gas emissions.[8] Germany is on course to produce 1 Mtonnes/year by 2003 thanks to a zero duty rate on the fuel. There are several excellent examples of European countries increasing their usage of biodiesel:

- Germany has been producing biodiesel since 1992, does not tax the fuel and has plans for an annual production of 400,000 tonnes. There are over 700 filling stations in Germany selling biodiesel.
- Many French towns have buses running on a mixture of biodiesel and fossil diesel. It is distributed, amongst others by Elf and Total. In fact most fossil fuel diesel in France is mixed with biodiesel today.
- In Sweden it is sold in a mixture with fossil diesel. Also in Stockholm they have greatly cut pollution by using ethanol as a fuel additive.
- Public transport in Rotterdam, Copenhagen, Olso, Zurich, Luxembourg, Lisbon and Barcelona has used biodiesel with excellent results.

Biodiesel in the UK

Road transport is now the UK’s third largest source of CO_2 emissions. The Governments Climate Change Programme sets out an ambitious package of measures across all sectors, which is expected to reduce greenhouse gas emissions by 23% by 2010 relative to 1990. This will include a substantial reduction in the use of carbon rich fuels in the transport sector. In the UK over 500,000 ha of land are set aside yearly; it is feasible that much of this land could be used for oilseed rape production. Surprisingly, much of the oilseed rape production in the UK is actually used in other European states.

Biodiesel has been tested by several organisations in the UK, all of which demonstrated the suitability of biodiesel for general use. In the most recent budget the Chancellor of the Exchequer, Gordon Brown, announced that biodiesel would qualify for a 20p per litre tax rebate. This will mean a tax on biodiesel of about 25p per litre to come into effect after approximately one year. Although this was widely considered a step in the right direction pressure groups have indicated that they would prefer the duty on biodiesel to be more like 10p per litre (in some EU countries there is no duty on biodiesel). With a reasonable duty on biodiesel it is predicted that farming industry could provide between 5 and 10% of the UK diesel needs over the coming years.[9]

The future

The UK is perceived within the EU as dragging its heels behind the biodiesel programmes in other member states. However slowly, it seems that the political mood is changing, with recent announcements of the lowering of the fuel duty on biodiesel and other more positive signs regarding future use of biofuels.

The amount of farmland set aside yearly could be used to grow crops such as oilseed rape. Through calculation it has been estimated that up to 10% of the UK's diesel consumption could be accounted for by biodiesel derived from homegrown crops, which is a significant amount in terms of saving fossil fuels and CO_2 emissions.

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Chemical companies take energy management to heart

This article from the Energy Efficiency Best Practice Programme discusses the importance of chemical companies to take energy management to heart

Introduction

The advent of the climate change levy (CCL) in April 2001 has provided the impetus for many chemical companies to look again at how much energy is used on site. The chemical sector has now finalised the Negotiated Agreement with the Government and this means that chemical companies will benefit from an 80% discount on the CCL. However, to retain this discount in future years, chemical companies must make the agreed energy savings.

As many chemical manufacturing organisations are re-launching their energy management strategies, there is an increasing requirement for support and guidance. Managers must use both time and financial resources as effectively as possible and energy management should now be part of any good management system. Energy and utility costs are frequently viewed as an 'overhead' but they are actually a controllable cost. As with any commodity, energy cannot be managed effectively unless it can be closely measured. It is not enough to just have a meter at the site boundary. Fortunately larger companies, with sites that have several plants and other buildings, have extra meters for cost allocation purposes. This data can be used as a key part of the energy management process.

Energy management is also not just about one person doing all the work. It is important to educate the whole workforce, starting at management level. Information is the key. Making sure everyone gets the message will make the energy manager's job a lot easier. There is a host of information available within the Government's Energy Efficiency Best Practice Programme (EEBPP), to help energy managers make the best use of energy inputs. The EEBPP is pioneering

Solutia, a chemical company working for energy efficiency.

a new scheme that will provide specific support to larger chemical manufacturing sites. This takes the form of ‘Partnerships’ between the site and EEBPP, who provide energy audits, training seminars, literature and technical help. The partnership approach is based on discussions between the site and specialists from the EEBPP who ensure that the events are ‘tailor made’ to suit the site’s specific requirements. This advice, when combined with the company’s own expertise, turns potential energy savings into improved profits as well as reducing environmental impact.

Solutia takes free advice

Solutia UK Ltd. operates a chemical manufacturing plant at Newport, South Wales, with seven production plants using organic and/or inorganic processes. Techniques used at the plant include pyrolysis, esterfication and hydrogenation, and the plant operates on a 24-hour shift pattern. The company produces several chemicals such as organic phosphonates, rubber chemicals, phosphate esters and a plasticiser used as the safety interlayer in car windscreens. Solutia recognised that there was plenty of scope for energy reductions at its Newport site. So, the company called on the EEBPP to help them form an energy management team and disseminate the necessary information factory-wide.

David Lloyd, an EEBPP energy consultant worked with Solutia and created a tailor made programme of talks and discussions. ‘Since the seminar in December, with full attendance of a wide cross section of personnel, we have initiated an Energy Steering Group. The first meeting has been held and over 180 items have been prioritised for investigation or action,’ Keith Agnew, who heads the group, explained. He is encouraged to have such a wide cross-section of support.

The Steering Group has drawn up a long-term plan and set a timescale for actions. ‘Following the seminar, I have ensured that energy efficiency is an area that appears in each line production manager’s goals,’ said Keith Agnew. ‘This is not a one-off event, though, we must deliver energy reductions year-on-year, and make sure we have continuous sustainable improvement’. Keith Agnew is encouraged that managers are so willing to take the energy efficiency message on board. ‘Solutia greatly values the EEBPP’s support and guidance, especially after the success of the seminar last December,’ he said.

GETTING STARTED

GPG 200 *A Strategic Approach to Energy & Environmental Management*
GPG 190 *Energy Efficiency Action Pack*
Video VI 014 *The Bottom Line*
Interactive software *The Energy ManageMent Advisor - EMMA*"
Focus - *The Manager's Guide to Reducing Energy Bills*
ACBE 001 *Energy Saving Guide for Small Businesses*
Institute of Director's *Making Savings by Managing Energy - a Director's Pocket Book*

PLANNING & ORGANISING

GPG 119 *Organising Energy Management - Corporate Approach*
GPG 186 *Developing an Effective Energy Policy*
GPG 167 *Organisational Aspects of Energy Management*
GPG 200 *Assessing Energy Management*
GPG 119 *Energy Management Matrix*

Solutia created an inventory and database of the 506 motors in use on site, and defined a motors strategy. As a result, the company will either rewind or replace motors at the appropriate time. If motors are over sized, they will be replaced with a smaller motor. Process optimisation is also an important factor and some improvements were identified. However, as major changes were made a few years ago, the potential for further savings is not as great as in other areas, such as reducing the amount of compressed air used on site.

Solutia uses a large amount of compressed air and the Energy Steering Group carried out a basic leak survey at the end of 2000. The leak rate for the site was considered to be the industry average, and the industry average is high. This means that any energy used to produce leaked compressed air is wasted. ‘To date £60,000 per year of leaks have been identified and the majority have been fixed, with the remainder in a plan to address them when there is an opportunity,’ said Keith. ‘It is important to keep up general good housekeeping measures of tightening valves and turning the air supply off when not in use. We must be able to sustain this improvement into the future,’ he said.

The benefits of having a company-wide Energy Steering Group cannot be over-emphasised. Having managers from all areas gives a true site perspective. Savings that can be made in one place may have cost implications elsewhere. It is important to be able to consider all these aspects together and to have everyone involved. Having gained the commitment of the management team, Keith is now very keen to get the message across to all site staff. ‘This year I will be creating a special topic for line manager meetings that will raise awareness and the importance to us all of energy efficiency. Ultimately, I would like to think we could have 250 energy managers here at Solutia,’ he said.

The EEBPP is able to help chemical companies set up an energy management strategy and support managers in implementing it. Free site-specific advice is provided through dedicated energy efficiency advisers. Several free publications are also available through the Environment and Energy Helpline Tel: 0800 585794, and the most relevant are listed in the box. Alternatively, visit the EEBPP website http://www.energy-efficiency.gov.uk for more details of the services offered.

For more information please contact: Kathryn Stubbing, IMS Public Relations (Tel. 01672 520788; Fax 01672 520789) or Elena Stewart, ETSU (Tel. 01235 433967; Fax 01235 433906).

Towards greener disposal of waste cathode ray tubes *via* ultrasonically enhanced lead leaching

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The disposal of waste cathode ray tubes (CRT) from old televisions and discarded computer monitors is rapidly becoming an issue of growing environmental concern due to the leaching of lead and other toxins by groundwater from landfill sites. Imminent legislation in both the EU and the USA is likely to demand much stricter control on the disposal of such hazardous electronic equipment, with a drive towards lead removal prior to landfill and/or recycling. This paper describes the use of power ultrasound to facilitate the removal of lead from the heavily-leaded CRT glass *via* an accelerated leaching protocol, with the aim of producing a lead-free product for greener disposal or more ideally for glass recycling purposes. The paper also describes the use of cathodic stripping voltammetry at a boron-doped diamond sensor, as a quick, easy and cost-effective technique for monitoring the rate of lead released from the CRT glass into a mildly acidic leachate.

Introduction

The problem of cathode ray tube (CRT) disposal from old televisions has slowly been increasing since the origin of commercial 'TV' towards the end of the 1920s and on through the post-war boom of the late 1940s, as the availability of increasingly affordable and ever-improving black and white, and then colour models from the mid-1950s, steadily progressed around the globe.[1,2] However, the requirements for CRT disposal started to grow at a rapidly increasing rate around twenty years ago with the birth of the 'desktop' personal computer (PC). As processor power soared, so the accompanying peripheral technology also improved dramatically, to such an extent that the replacement of the entire desktop and monitor every couple of years became commonplace. The overwhelming majority of discarded monitors, are buried in landfill sites and form the basis of a potential environmental time-bomb. Also, with the falling cost and hence increasing popularity of high-definition television sets and flat-screen PC monitors, the number of discarded CRT-based screens is set to rise sharply.

Both TV and PC-monitor CRTs contain a number of toxic substances including mercury, cadmium and dioxins. However the element of main environmental concern is lead, which is present in high levels, predominantly in the glass envelope of all colour CRTs (monochrome CRT glass has been shown to contain very little lead[3]). Lead, which is a particularly toxic and accumulative heavy metal poison,[4] affects the majority of pathways in the processes of haem synthesis and porphyrin metabolism,[5] and can be steadily leached from crushed CRTs and other electronic equipment in landfills by acidic ground water, presenting many potential health hazards, including serious damage to the endocrine and nervous systems.[6] The majority of CRTs are currently disposed of through the traditional solid waste management method of landfilling; some also by incineration, but even these 'waste-to-energy' facilities result in the environmentally problematic concentration of heavy metals in the ash. Currently, there exists only a very limited number of facilities for CRT recycling, resulting in a negative net value for used CRT glass. However, any system which could be developed to facilitate the removal of the leachable lead from CRTs prior to landfill would offer obvious environmental benefits, especially as the 'cleaned' glass itself already has potential uses as glass cullet for new CRTs or as a silica-based fluxing agent in lead-acid battery recycling.[7]

In the UK it has been estimated that at least a million PCs are sent to landfill each year, forming a significant part of the near 30 000 tonnes of lead from waste electronic equipment accumulating annually in UK landfill sites.[8] In the United States, it was predicted for the year 2000 that CRTs would represent around one third of discarded electronics tonnage, with their lead content equivalent to approximately 80% of the toxic metals found in this waste.[9] Approximately 100 million new PCs are sold globally each year and recycling issues could soon become the responsibility of the initial product supplier. The US is still in the process of formulating a *national policy*

Green Context

Green Chemistry is most commonly associated with environmentally benign chemical manufacturing and environmentally compatible products but green chemical technology needs to be applied to a very wide range of processes in modern society. This article describes the greening of a process that has become essential in today's 'throwaway' society. Remarkable numbers of cathode ray tubes from televisions and computer monitors are currently being discarded and at an accelerating rate. Apart from raising fundamental questions about wasted resources, we have to address the fact that these CRTs contain several toxic components which can be expected to enter the environment on their disposal to land fill sites. It has been estimated that in the US for example, some 80% of the toxic metals found in electronics waste would have originated from the CRTs. It is essential that we have effective methods for removing those toxic substances that are not themselves damaging to the environment. Here a greener method of removing the worst of those toxic substances, lead, from waste CRTs is described. It shows how power ultrasound can be used to remove lead from heavily-leaded CRT glass giving a product that can be safely recycled for further use. ***JHC***

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towards classing CRTs as a hazardous waste for disposal, however, CRT dumping is already banned in Massachusetts.[10] The issue is also set to become significantly more high profile throughout the EU, as the recently proposed directive on Waste Electrical and Electronic Equipment (WEEE), which aims to pin the responsibility for CRT and other electronic equipment recycling upon the original manufactures looks set for ratification over the next few years.[11] The inevitable introduction of similar new legislature around the globe will clearly drive the need for new, efficient and more responsible CRT clean-up technologies.

The technology behind the colour CRT has remained largely unchanged for the past 100 years [see Fig. 1(a)]. Basically, a colour CRT is a high vacuum, high mechanical integrity sealed glass bottle, the base of which forms a CRT's screen. High voltages are used to accelerate electrons from an electron gun, containing three cathodes—one for each colour: red, green and blue—in the bottle neck, towards luminescent 'phosphors' deposited on the inside of the faceplate, which convert the energy of the electrons into light. The electron beam, drawn towards the CRT's screen by a powerful, positively charged anode, passes through a perforated metal 'shadow mask' which stops incorrectly aimed electrons from illuminating the wrong colour phosphor. An electromagnetic deflection yoke is used to focus and rapidly move the electron beam around the screen to form the 'picture' that we see.

A simplified diagram of where the lead is usually situated in the various parts of a typical colour CRT is shown in Fig. 1(b). Throughout the entire neck and funnel section, the high density glass matrix is heavily leaded, typically 22–25% Pb, to absorb the X-rays which are emitted as the electrodes decelerate after being fired from the electrode gun towards the CRT screen. This is where the bulk of the mass of lead in a CRT is to be found. The lead oxide/organic binder solder, which is used in the 'frit' to weld the faceplate and the funnel of the CRT together in a high temperature sealing process called a Lehr bake,[12] contains the highest concentration of lead in a CRT construction, typically 70–85% Pb. Although lead is known to leach quite readily from this softer material using the EPAs standard Toxicity Characteristic Leaching Procedure (TCLP),[13] the amount of material in the frit is very small compared to the mass of leaded-glass contained in the neck and funnel. The faceplate typically contains very little, if any lead (0–3% Pb). In terms of CRT recycling, all non-glass parts of a CRT construction can easily be removed, with the metal parts and the electronics, essentially the copper coils within the deflection yoke, then available for straightforward metal recovery. What remains is a fragmented collection of glass with a range of lead content, which is currently destined for landfill. Any system offering green removal of lead from waste CRT glass would therefore be highly desirable.

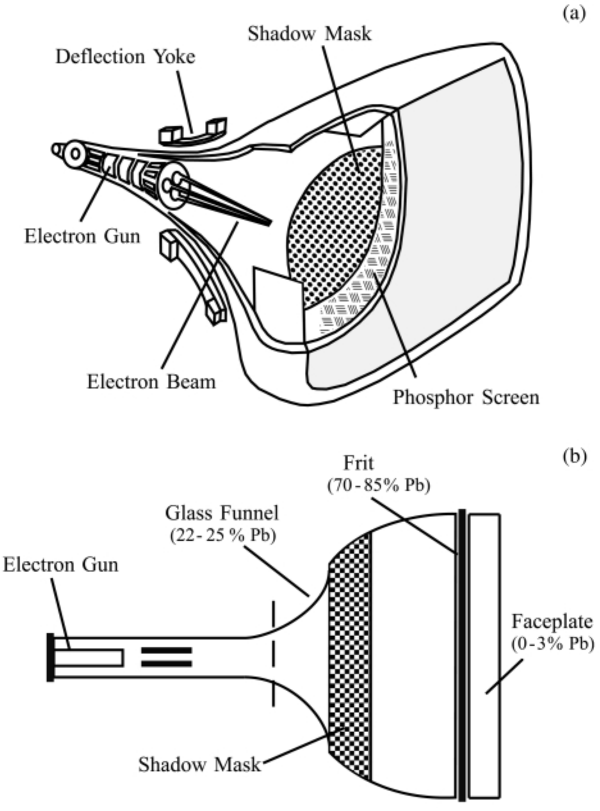


Fig. 1 Schematic diagram showing (a) the general construction and (b) the lead contents of a typical colour cathode ray tube monitor.

One of the cleanest ways of removing undesirable elements from solid materials is *via* some kind of leaching protocol. A number of chemical and biological agents have been used previously to facilitate the removal of harmful contents from the solids.[14,15] However, these often produce a new waste stream, so care must be taken when choosing a leaching agent so as to minimise further damage to the environment. The leaching of solid samples in static water, although requiring little if any energy input, is generally, a very time-consuming procedure. In general, to accelerate the leaching processes, a range of physical agitation methods have previously been employed including mechanical shaking,[13,16–18] stirring,[19,20] vortexing,[21] heating,[22] percolation[23,24] and microwave irradiation.[25–27] However, the technique which offers some of the largest increases in leaching efficiency from a range of complex solid matrices is sonication.[28–31] Recently, ultrasound has also been used specifically for heavy metal leaching from various environmental biocollectors[32,33] and even human hair.[34] The application of power ultrasound to solid leaching produces a very useful accelerated leaching method in which a number different physical properties can contribute to the overall effect. Amongst the most influential effects of the application of ultrasound towards 'solid in liquid' leaching are acoustic streaming, which can aid the mass transport of species away from the solid / liquid interface and cavitation, which results in micro-jetting (rapid bursts of liquid 'jets' as bubbles close to the solid/liquid interface collapse), which can cause cleaning, pitting and activation of a solid surface.[35]

The use of ultrasound is not limited, however, to laboratory-scale processes, although the invariably larger solution volumes required for industrial methodologies will usually require careful consideration of the type of reactor employed. *Whistle* reactors have generally been used for ultrasonic homogenisation in the food industry, although the technique has also been *scaled-up* for the dispersion of pyrogenic silica in liquid resins, at rates up to 12000 dm^{-3} h^{-1}.[36] Murry reported numerous large-scale ultrasound applications for the use in the chemical, textile, pharmaceutical, cosmetic and food industries.[37] Hunicke described the application of large scale magnetostrictive transducers with power ratings in the tens of kW and flow rates of thousands of litres per hour, to large-scale cleaning, aluminium soldering and coal ore beneficiation.[38] Only recently, in a similar environmental vain to the ideas proposed in this article, the application of ultrasonic irradiation for waste-water treatment and remediation of contaminated soils has been outlined.[39]

In this study, we aim to investigate the suitability of ultrasonically enhanced leaching towards the removal of leachable-lead from waste CRT glass, over a range of particle sizes, in order to produce a potential greener route for CRT disposal and/or recycling. In order to quantify the efficiency increase observed over silent leaching, ultrasonic leaching is compared side-by-side with silent *stirred* leaching, so as to eliminate the simple agitation effects observed under sonication. The paper also describes the use of a simple, clean and cost-effective cathodic stripping voltammetry technique using a boron-doped diamond probe for lead analysis of the CRT leachate.

Experimental

Reagents and CRT glass samples

The reagents used were of analytical grade of the highest commercially available purity: lead nitrate (99.999%) and nitric acid (70% double distilled) were supplied by Aldrich. All solutions were prepared using UHQ grade deionised water of resistivity not less than 18 MΩ cm (Elgastat, High Wycombe, Bucks., UK). A Mitsubishi Colour Picture Tube (Electric Corp. Japan, M34JBF02X01, 4F0154) was used to prepare samples of CRT glass for lead leaching. A representative selection of glass pieces were taken from throughout the neck and funnel section and were reduced in size by repeated crushing and sieving to give a range of particle sizes: 2–5 mm, 1–2 mm, 0.5–1 mm and $<$ 0.5 mm, with the smallest having the appearance of a fine powder.

Equipment and instrumentation

A jacketed glass cell, allowing circulation of thermostatically controlled (22 ± 2 °C) cooling water around the leaching experiment, was used for both the leaching and the subsequent voltammetric Pb^{2+} measurements (Fig. 2). For all experiments, to facilitate electrochemical measurement of the lead ions leached from the CRT glass, the cell contained an industrially-polished, boron-doped diamond film electrode ($5 \times 5 \times 0.6$ mm^3, supplied by DeBeers Industrial Diamond Division, Ascot, UK) mounted in a Teflon™ holder, as the working electrode, a saturated calomel electrode, SCE (Radiometer, Copenhagen, Denmark) as a reference electrode and a spiral-wound platinum wire as a counter electrode. Electrochemical measurements were conducted using a PGSTAT20 Autolab computer controlled potentiostat (Eco-Chemie, Utrecht, Netherlands).

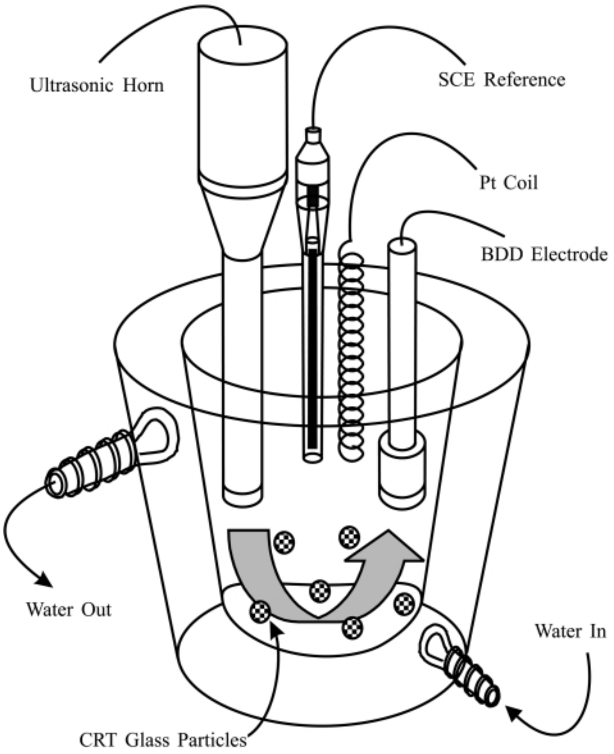


Fig. 2 Schematic diagram of a jacketed glass cell used for sono-leaching and sonoelectroanalysis.

For the *sono*-leaching experiments, ultrasound was delivered into the cells *via* a 13 mm titanium-alloy tip attached to an extended probe of a VXC400 model ultrasonic horn (Sonics and Materials, USA), capable of emitting 20 kHz ultrasound at intensities up to 63 W cm^{-2} (determined calorimetrically[40,41]). During the *sonoelectroanalysis* measurements, the need for bipotentiometric[42] control of the titanium horn was eliminated by insulating the transducer from the probe with a Teflon™ disk, and connecting the two with a screw-thread machined from Delrin™. The horn was positioned 15 mm from the bottom of the cell and adjacent to the working electrode, so as to allow acoustically driven circulation of leachate *through* the CRT glass samples during the leaching cycles and towards the face of the working electrode during the electrochemical measurements. Ultrasound of 14 W cm^{-2} intensity was applied for all sono-experiments in order to minimise localised heating of solution and prolong the glass cell and electrode life.

During the silent/stirred leaching experiments, the ultrasonic probe was removed from the cell and replaced with a magnetic stirrer bar, with the cell itself placed upon a magnetic stirrer. To achieve a similar agitation effect to that observed during the sono-leaching experiments, so as to eliminate the simple stirring effect of ultrasound in terms of its enhanced leaching abilities, the magnetic stirrer was set at 400 rpm for all silent/stirred leaching experiments. A 400 rpm stirring speed ensured good chaotic mixing of the glass CRT particles and created a sustained and reproducible hydrodynamic flow of leachate over the face of the BDD sensor, replacing the acoustic flow described earlier and hence allowing sensitive Pb^{2+} detection without the need for applying ultrasound to the cell.

Results and discussion

Electrochemical monitoring of Pb^{2+} ion release

The rate of lead ion release from the crushed CRT glass samples was measured using cathodic stripping voltammetry at the boron-doped diamond sensor. The background to and development of the technique by our group has been reported previously.[43,44] In summary, aqueous Pb^{2+} ions leached from the CRT glass into the 0.1 M HNO_3 supporting electrolyte were accumulated (with the aid of acoustic streaming or stirring) on the BDD electrode at a potential of +2.07 V *vs.* SCE forming PbO_2 [see Fig. 3(a)], after pre-deposition of a small amount of metallic Pb^0 at -1.0 V *vs.* SCE. The deposition times were varied depending upon the release rate of lead from the CRT glass samples; 5 s pre-deposition, 10 s PbO_2 deposition for the powder ($<$ 0.5 mm diameter) up to 30 s pre-deposition, 60 s PbO_2 deposition for the largest CRT particles (2–5 mm diameter), so as to avoid ‘overload’ of the BDD electrode. After lead dioxide deposition, quantification was achieved by ‘cathodically’ sweeping the potential of the working electrode from +1.65 to 0.0 V *vs.* SCE, with the peak current of the resultant stripping peak at a potential of approximately +1.2 V *vs.* SCE [see Fig. 3(b) for example] being a direct measure of the amount of PbO_2 deposited. The amount of lead in solution was quanitified at the end of each leaching experiment by adding aliquots of a suitably diluted Pb^{2+} standard solution to the cell after the final leaching cycle (described later) in a typical ‘standard addition’ experiment [see Fig. 4(a) for typical standard addition voltammetric responses), with the Pb^{2+} ion concentration in solution being obtained from extrapolation of the resultant calibration curve [Fig. 4(b)].

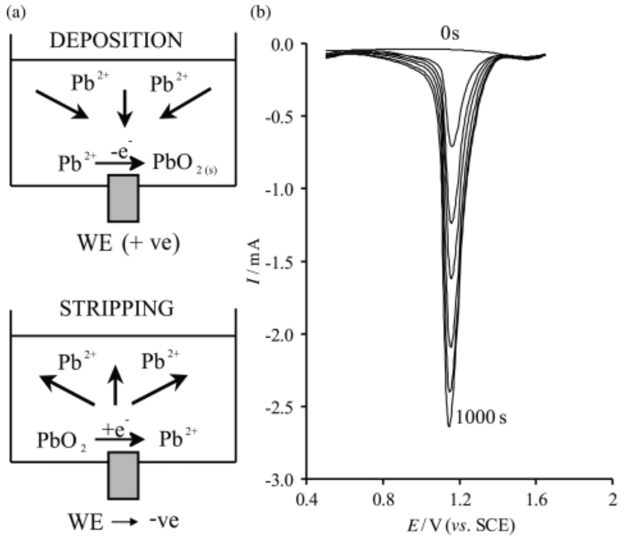


Fig. 3 (a) Schematic diagram showing the deposition and stripping steps of cathodic stripping voltammetry (CSV) of Pb^{2+}. (b) Typical voltammetric traces for CSV analysis of Pb^{2+} leached from cathode ray tube (CRT) glass. Example: sono-leach of < 0.5 mm CRT glass in 0.1 M HNO_3. Experimental parameters: 5 s pre-deposition of Pb^0 at −1.0 V (*vs.* SCE), 10 s insonated PbO_2 deposition at +2.07 V (*vs.* SCE), stripping scan (SWV) from +1.65 to 0.0 V (*vs.* SCE) at 50 Hz, step potential = 10 mV, amplitude = 100 mV.

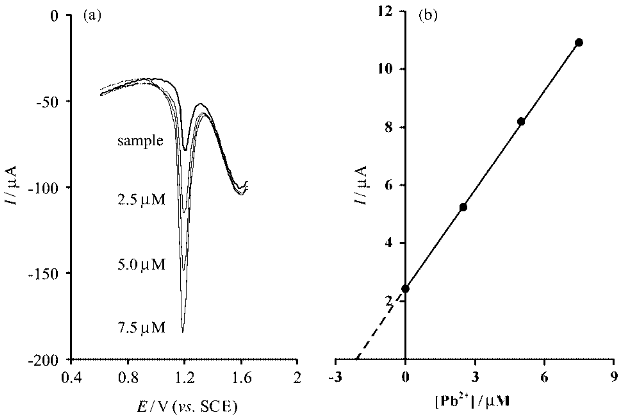


Fig. 4 Example data from silent (stirred) leaching of 1–2 mm cathode ray tube (CRT) glass particles in 0.1 M HNO_3: (a) voltammetric traces obtained from Pb^{2+} standard addition experiment [experimental parameters as Fig. 3(b)], (b) standard addition calibration plot to obtain final Pb^{2+} concentration: slope = 1.104 µA μM^{-1}, R^2 = 0.9999.

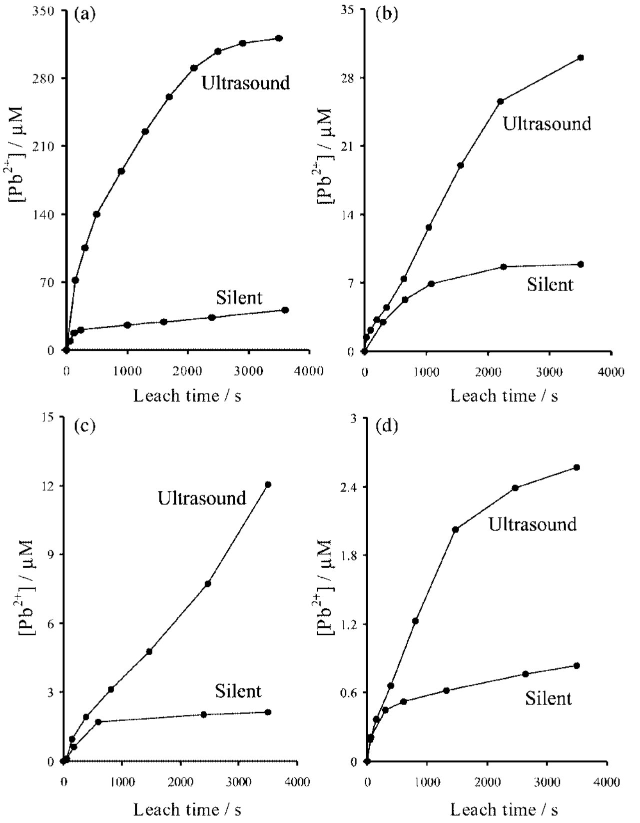


Fig. 5 Sono- and silent (stirred) leaching profiles of cathode ray tube (CRT) glass particles of (a) < 0.5 mm, (b) 0.5–1.0 mm, (c) 1.0–2.0 mm and (d) 2.0–5.0 mm size, in 0.1 M HNO_3.

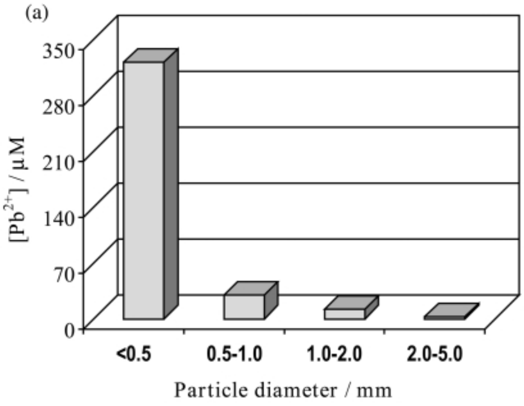
Leaching experiments

For all leaching experiments, approximately 1 g of crushed CRT glass of a particular particle size was accurately weighed and placed into the glass cell with 20 ml of 0.1 M HNO_3, which acted as both the supporting electrolyte for the electrochemical Pb^{2+} determinations (described earlier) and provided the required acidic pH for heavy metal leaching.[31,45] To facilitate accelerated leaching, the cell was then subjected to either continuous insonation or stirring, over a time period of approximately 1 h for each sample, with Pb^{2+} measurements taken at regular intervals.

The first observation from the 'ultrasound *versus* silent leaching' experimental results depicted in Fig. 5 is the dramatic increase in Pb^{2+} leaching rate upon insonation. After leaching for 1 h there was an average seven-fold increase in the amount of lead leached into solution, across all of the particle sizes tested, with an eleven-fold increase observed for the smallest particle size [powder, < 0.5 mm, Fig. 5(a)]. It is also apparent from these 'leaching profiles', that the Pb^{2+} ion release rate rapidly tails off during the silent leaching experiments after approximately 5–10 min, whereas lead is leached at a relatively constant rate throughout the lifetime of the sono-experiments. Only in the case of the CRT glass powder (< 0.5 mm) does the rate tail off dramatically around 2500 s, where a plateau of Pb^{2+} concentration seems to have been reached, indicating that all of the available *leachable* lead may have been removed. This will be discussed in more detail below.

Particle size is the second variable which has a marked effect upon the amount of lead which can be leached from crushed CRT glass. As one would expect, reduced particle size and hence increased surface area allows the removal of substantially more lead (see Fig. 6) however, the effect is even more apparent when the leaching is carried out under insonation. After 60 min leaching, the final Pb^{2+} concentration measured during the sono-leaching experiment fell by 91% as the particle size was increased from < 0.5 to 0.5–1 mm, whereas a 78% decrease was observed for the same particle size increase during the silent/stirred experiments.

The remarkable increases observed in Pb^{2+} leaching rates over silent/stirred leaching can be explained in terms of the ability of ultrasound to allow deeper penetration of the leachate into the CRT glass, than under silent conditions. This likely occurs predominantly *via* cavitational erosion of the particle surface,[35] with visual observation of small bubbles violently 'fizzing' across the larger particle surfaces under insonation. The effect of this erosion can be seen in Fig. 7, where atomic force microscopy (AFM) images of the surface of a single 5 mm CRT glass particle, held stationary opposite the tip of the ultrasonic horn at a distance of 15 mm and previously polished to give a uniform surface for AFM imaging, are shown before and after 300 s of insonation. Ignoring the 'scratches' from polishing and defect-pits on the original smooth surface, the post-insonation images clearly show a rougher, more eroded surface, after only 10% of the time used, compared to the earlier-described leaching tests. The second effect of ultrasound which again increases the efficiency of lead leaching from CRT



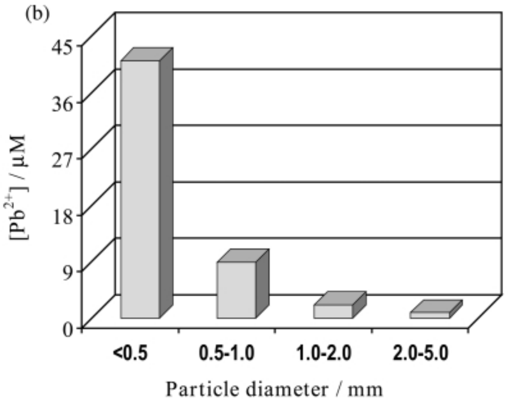


Fig. 6 Bar graphs showing the final Pb^{2+} concentration after 1 h from (a) ultrasonic and (b) silent (stirred) leaching of cathode ray tube (CRT) glass particles in 0.1 M HNO_3.

glass, is further reduction of particle size through mechanical fracturing of the brittle CRT glass. This was observed visually, under test conditions, as chunks were seen to be fractured off the larger particles, and also under scanning electron microscopy (SEM) imaging, where a smooth uniform surface prior to insonation [Fig. 8(b)] was seen to become more angular and scattered with many smaller 'splinters' [Fig. 8(c)] similar in size to the particles constituting the 'powdered' CRT glass [Fig. 8(a)], which allowed rapid Pb^{2+} leaching.

Finally, multiple repeat-leaching experiments (leach, filter, dry and re-leach) using both ultrasound and stirred leaching were carried out on CRT glass 'powder' ($<$ 0.5 mm) samples. In order to estimate how close to total leaching of lead each technique comes (see Fig. 9), it was assumed for the sono-leaching of the powder, that nearly all of the readily leachable lead has been removed after 60 min of leaching, at the point where the concentration profile plateau is observed. After this time, there was approximately a 92% reduction in leachable lead between the first and second leaches, with a further 61% reduction observed between the second and third. This was also accompanied by a significant reduction in the Pb^{2+} ion release, as the slopes of the first, second and third leaching profiles, approximately 102, 7.5 and 3.1 nM s^{-1} respectively, rapidly tended towards zero. Repeat-leaching of powdered CRT glass under silent conditions, although at much lower Pb^{2+} concentrations, initially shows a similar stepwise reduction in the amount of lead removed. However, most of this is achieved in the first minute of leaching, as the lead on the very surface of the finest particles is leached, after which the release rates reduce much less rapidly than in the ultrasound experiment (approximately 6.1, 3.4 and 1.3 nM s^{-1} for the first, second and third leaching profiles respectively) as lead is very slowly leached from deeper within the material.

It seems quite clear from these results that sono-leaching of powdered CRT glass, even after only a 1 h leaching cycle, can be used to remove over 90% of the leachable lead, with the

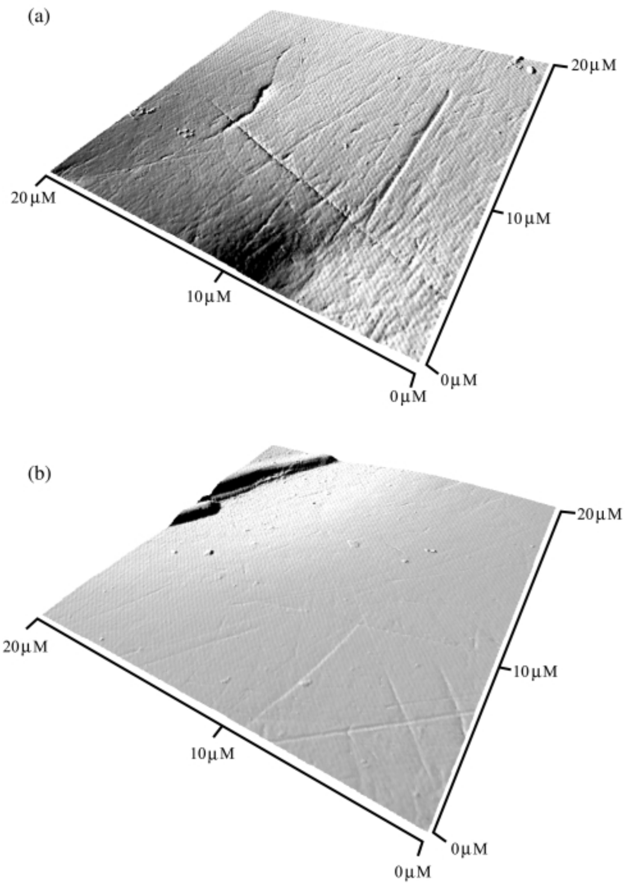


Fig. 7 Atomic force microscopy (AFM) images of a single cathode ray tube (CRT) glass particle (a) after 300 s insonation (horn–particle separation = 15 mm) in 0.1 M HNO_3 and (b) before insonation.

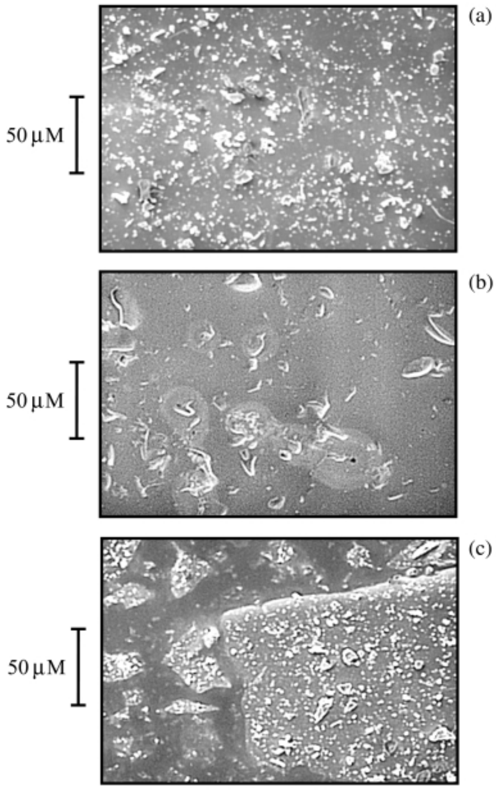


Fig. 8 Scanning electron microscopy (SEM) images of cathode ray tube (CRT) glass particles: (a) untreated $<$ 0.5 mm 'powder', (b) 5 mm particle pre-insonation and (c) 5 mm particle after 300 s insonation [experimental details as Fig. 7(a)].

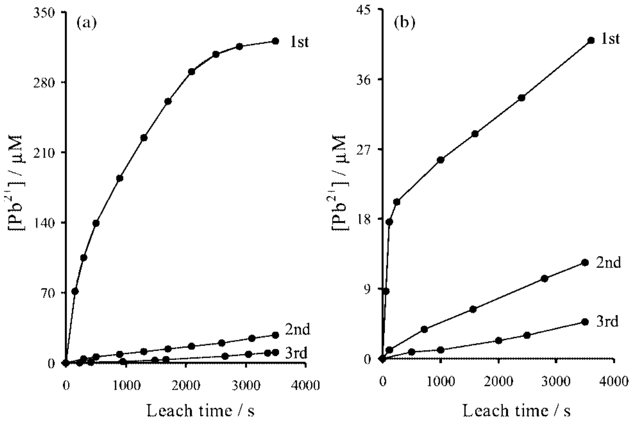


Fig. 9 Multi-leach profiles, showing Pb^{2+} ion release from first, second and third leaching of a single cathode ray tube (CRT) glass 'powder' (< 0.5 mm diameter) sample using (a) sono- and (b) silent (stirred) leaching.

remainder slowly released upon further insonation. As a comparison, silent leaching yields only a fraction of the available lead and the remainder would take many hours, if not days to leach to the levels achievable using ultrasound.

Conclusions

Ultrasound has been shown to be a valuable tool with regards to enhancing the efficiency of lead leaching from waste cathode ray tube (CRT) glass. Leaching rates over an order of magnitude greater than those obtained using silent/stirred leaching of powdered CRT glass were observed under insonation, allowing removal of over 90% of the leachable lead after only 1 h of sono-leaching. The release rate of lead into an mildly acidic leachate was found to tail off rapidly with increased particle size, however, ultrasound has been show to facilitate greatly accelerated Pb^{2+} leaching through a combination of cavitational erosion and mechanical fracturing of the brittle CRT glass, for all particle sizes tested.

The results presented here are clearly prove the feasibility of this procedure under laboratory-scale conditions, however, the potential scale up of the technique would be the ideal goal. Due to its brittle nature, CRT glass is easily crushed into a fine powder, so this would help to keep down sample preparation costs. Also, commercial ultrasonic equipment is readily available, as are large-scale ultrasonic industrial processes. Although some kind of process optimization would likely be required particular to this system, scale-up of the methodology described here can easily be envisaged, facilitating the accelerated leaching of lead from large amounts of disposed CRT glass. In a worse case scenario, the cleaned glass might be available for greener landfill, but ideally it could be used for various glass recycling purposes. Also, as an added benefit, the leached Pb^{2+} ions in the dilute nitric acid leachate are already in an ideal form for electrochemical recovery of metallic lead at a suitable cathode.

The potential environmental benefits of this technology are considerable.

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Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation

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A series of hydrophilic and hydrophobic 1-alkyl-3-methylimidazolium room temperature ionic liquids (RTILs) have been prepared and characterized to determine how water content, density, viscosity, surface tension, melting point, and thermal stability are affected by changes in alkyl chain length and anion. In the series of RTILs studied here, the choice of anion determines water miscibility and has the most dramatic effect on the properties. Hydrophilic anions (*e.g.*, chloride and iodide) produce ionic liquids that are miscible in any proportion with water but, upon the removal of some water from the solution, illustrate how sensitive the physical properties are to a change in water content. In comparison, for ionic liquids containing more hydrophobic anions (*e.g.*, PF_6^- and $N(SO_2CF_3)_2^-$), the removal of water has a smaller affect on the resulting properties. For a series of 1-alkyl-3-methylimidazolium cations, increasing the alkyl chain length from butyl to hexyl to octyl increases the hydrophobicity and the viscosities of the ionic liquids increase, whereas densities and surface tension values decrease. Thermal analyses indicate high temperatures are attainable prior to decomposition and DSC studies reveal a glass transition for several samples. ILs incorporating PF_6^- have been used in liquid/liquid partitioning of organic molecules from water and the results for two of these are also discussed here. On a cautionary note, the chemistry of the individual cations and anions of the ILs should not be overlooked as, in the case of certain conditions for PF_6^- ILs, contact with an aqueous phase may result in slow hydrolysis of the PF_6^- with the concomitant release of HF and other species.

Introduction

The continued use of large quantities of organic solvents as liquid media for chemical reaction, extraction, and formulation is a major concern in today's chemical processing industry. The perceived deleterious effects of these materials on human health, safety, and the environment combined with their volatility and flammability has lead to increasing pressure for minimizing their use both from a public relations and a cost perspective. Concepts, such as Environmental Stewardship,[1] have placed a renewed emphasis on careful solvent selection and a search for less harmful alternatives. In the past, the emphasis in industrial chemistry was placed on product yield and quality. Increasingly, solvent use during manufacture is viewed in terms of avoiding the costs associated with disposal, legal liabilities, and regulatory constraints.[2]

Recent regulatory controls have aggressively targeted the reduction of the volume of industrial pollutants, a major component of which comprise spent solvents unsuitable for recycling. Approaches to reduce the reliance on traditional solvents will be of tremendous importance in cleaning up industrial problems. Currently, treatment of solvent-laden wastes is a cost borne by industry, human health, and the environment. Although alternative approaches such as heterogeneous catalysis[3,4] and aqueous reaction media exist,[5–7] they may not represent generic solutions to these problems.

The ideal opportunity for waste reduction occurs before any reagents are mixed, during process design. In this approach, basic chemistry must play an important role in formulating alternative manufacturing processes with minimized hazards and decreased waste generation. This shift in the manufacturing paradigm is the basis of 'Green Chemistry', rather than pollute and remediate.[8] Green Chemistry also proposes optimized synthetic methodologies for high product yields and the generation of substances that offer little harm to the environment. In view of the heavy reliance on organic solvents in current manufacturing processes, the development of new technologies for pollution prevention can assist in the reduction of VOC usage and the associated volatility, environmental, and human health concerns that accompany exposure to organic solvents.

Green Context

Ionic liquids (ILs) are non-volatile, non-flammable and thermally stable solvents and as such as very promising replacements for the traditional volatile organic solvents. Their quite rapid emergence as alternative solvents has involved a rapidly growing number of examples of application but the understanding and study of their physical properties has lagged behind. It is very important that we accumulate a substantial body of physical data for these fascinating substances so that their true potential as solvents can be realised. Here the effects of the alkyl chain length of the cation and the identity of the anion on the key properties of hygroscopicity, density, viscosity, surface tension, melting point and thermal stability are studied. The anion identity is shown to be of foremost importance. ***JHC***

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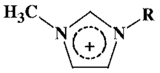
Ionic liquids (ILs) as solvents

One of the most promising areas of research in new 'green' technologies is the application of neoteric solvents,[9] a category which includes supercritical CO_2,[10–12] aqueous biphasic systems,[13–15] and ionic liquids (ILs).[16–20] ILs offer a highly solvating, yet non-coordinating medium in which a number of organic and inorganic solutes may be dissolved.[12,21] In the ideal case, ILs are non-volatile, non-flammable, have high thermal stability,[22] and are relatively undemanding and inexpensive to manufacture. Many ILs fulfill these requirements and are liquids over a wide temperature range (some can exceed 300 °C). Melting points as low as −96 °C are known,[23] thus the usable liquid range may cover that used for conventional synthetic chemistry and low temperature extractions.

In the current understanding, ILs contain large, organic cations (Fig. 1) with a variety of anions and melt at or below about 150 °C (adopted as an arbitrary upper temperature limit for ionic liquids). We prefer to work with those ILs which have a liquid phase at ambient temperature and refer to these as room temperature ionic liquids (RTILs). ILs are usually composed of organic cations such as quaternary ammonium cations,[24,25] heterocyclic aromatic compounds,[26] pyrrolidinium cations,[27] derivatives of natural products,[28] and some more esoteric cations.[29,30] The properties of both cation and anion are useful tools for fine-tuning the properties of the resulting IL for desired 'solvent' properties. Clearly, many different ILs may be synthesized having a wide range of physical and chemical properties.



$CH_3CH_2CH_2CH_2 = [C_4mim]^+$
$CH_3CH_2CH_2CH_2CH_2CH_2 = [C_6mim]^+$
$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2 = [C_8mim]^+$

Fig. 1 Formula of 1-alkyl-3-methylimidazolium cations.

The urgency surrounding the chemistry of ILs is attributed to their unique set of chemical and physical properties. The low melting nature of ILs can be engineered by combining cationic and anionic species to produce salts that, largely due to the asymmetric cations, have low lattice energies. The overall properties of ILs result from the composite properties of the cations and anions and include those that are superacidic,[20,31,32] basic,[33] hydrophilic, water miscible,[34,35] water immiscible and hydrophobic.[20,32,34] The anion is currently used to control the water miscibility, but the cation can also influence the hydrophobicity[16,19,34,36] or hydrogen bonding ability.

Although the field of electrochemical applications of certain ILs is more mature, new RTILs have performed well in catalysis and synthetic experiments, oftentimes yielding unanticipated results, such as facilitated product recovery, enhanced separation,[20] or a preference for a particular isomer of the product.[37,38] The low temperatures typical of reactions in these systems tend to limit dissociation, disproportionation, and degradation reactions such that stability of otherwise transient species is often extended in the ionic environment. With an IL such as $[C_4mim][BF_4]$, Beckmann rearrangement reactions can be performed under milder conditions to avoid the deactivation usually encountered in those reactions.[39]

We have demonstrated the utility of certain RTILs in a variety of separations with several RTILs which have solvent characteristics suitable for their incorporation in place of traditional volatile organic compounds (VOCs) in liquid/liquid separations.[16,18] For example, with a series of organic solutes, we have shown that the solute affinity for the RTIL ($[C_4mim][PF_6]$) phase increases in correlation with the solute's 1-octanol/water log *P* value (a traditional hydrophobicity probe).[16] Liquid/liquid extraction and reactive separations (where the reagents and products differ in IL solubility) offer excellent opportunities to reduce the reliance on VOCs in many industries.

In this paper we investigate and compare the properties of RTILs containing various 1-alkyl-3-methylimidazolium cations, due to the increasing number of reports in the literature utilizing RTILs of this type. Here the variations in alkyl chain, in conjunction with different anions, lead to a large matrix of materials. Characterization in terms of physical and chemical properties is thus an important first step toward their ultimate application.

Chemical and physical properties of new solvents

Before considering a new solvent for incorporation into an industrial application, a fundamental understanding must be established for the chemical and physical properties of the solvent. Ideally, if a new solvent is to be introduced as a 'green' solvent, it would be an improvement over the solvents currently available. Optimal physical properties would include low viscosity to facilitate mixing and a large density difference in comparison to other process fluids to hasten phase separation. Chemically, the solvent would have a high capacity for the solute. To encourage widespread use of the solvent, it would be inexpensive to produce, recyclable, and robust to endure various processing environments.

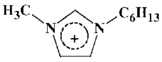
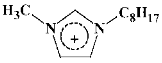
Of most interest to us at present are ionic liquids that are liquid at room temperature and represent potential replacements for traditional volatile organic solvents in separations processes. Recent developments have seen the investigation of classes of ionic liquids that are not only liquid at room temperature, but also air and water stable[34] which further increases the range of ionic liquids suitable for industrial application. Several physical and chemical properties of organic liquids merit their investigation when attempting selection for a particular application such as their use in dissolution or reaction media for various solutes.

Physical properties such as melting point, boiling point, density, and viscosity, are related to the mechanics and engineering components associated with a process. For example, densities, viscosities, and surface tensions will determine important parameters including rates of liquid–liquid phase separation, mass transfer, power requirements of mixing and pumping. Other physical properties, such as refractive index, are related to certain chemical properties despite providing a bulk property description. Chemical properties such as the structuredness, polarity, and relative hydrogen bonding donating and accepting ability are more obviously related to the molecular chemistry of their application.[40] Due to the obvious intermolecular interactions that these parameters measure, these chemical properties are belived to play a major role in determining solubilities, partition constants, and reaction rates.

Results

A series of hydrophilic and hydrophobic 1-alkyl-3-methylimidazolium salts of bis(trifluoromethylsulfonyl)imide $(Tf_2N)^-$, PF_6^-, BF_4^-, Cl^- and I^- (Table 1) were prepared and their physical properties determined. The tabular results have been organized first by the most hydrophilic cation, decreasing in the series butyl, hexyl, octyl, and then arranged by the perceived increasing hydrophobicity of the anion from Cl^-, I^-, BF_4^-, PF_6^- to Tf_2N^-. Hydrophobic RTILs were studied both after equilibration with water corresponding to the maximum water concentration at ambient temperature, and after a moderate drying procedure which removed most of the water. The hydrophilic RTILs studied here are completely water soluble and were studied only after the drying procedure and referred to as 'dried', although many still contain some water.

Table 1 Ionic liquid cations and anions used in this study

Cations		Anions	
	$[C_4mim]^+$	Hexafluorophosphate	PF_6^-
		Tetrafluoroborate	BF_4^-
		Halides	Cl^-, I^-
	$[C_6mim]^+$	Bis(triflylmethyl-sulfonyl)imide $N(SO_2CF_3)_2^-$	Tf_2N^-
	$[C_8mim]^+$		

Water content

It is readily apparent from Table 2, that in the small series of RTILs studied here, the identity of the anion greatly influences the water miscibility and, if hydrophobic, the extent of which water is miscible in that IL. This also appears to be a factor in controlling the extent to which the RTILs may be dried, or the difficulty involved in drying to very low moisture contents.

Certain precautions are sometimes necessary, however, to account for the chemistry associated with the cations and anions. RTILs containing the PF_6^- anion are sparingly water soluble, but when used in liquid/liquid separations from acidic aqueous phases, the PF_6^- may undergo hydrolysis to produce HF and PO_4^{3-}.[19] Other anions may be better suited for such applications.

The current generation of air and water stable IL which remain in the liquid state at close to room temperature, are free from many of the difficulties involved in the application of, for example, the haloaluminate salts. Nevertheless, as may be judged from Table 2, they may contain significant amounts of water or be entirely miscible with water. While in this series this property is largely conveyed by the hydrophobicity of the anion, the water miscibility of the BF_4^- RTIL depends on the length of the alkyl chain or the temperature of the system. Holbrey and Seddon reported that, for $[C_n mim][BF_4]$, those with $n < 6$ are water soluble, although to varying degrees.[23] $[C_4mim][BF_4]$ at room temperature is completely water soluble but, at 0 °C, the solubility decreases.[36]

The presence of water may have a rather dramatic affect on reactivity, not only in the new biotechnology applications which have started to appear,[41–43] but also in many synthetic schemes using IL reaction media. Water is present in all RTILs of the type we studied, even after a moderate drying procedure. Organic solvents are known to contain varying degrees of water, unless rigorous drying protocols and inert environments are employed. There is little evidence in the current IL literature that such precautions are being taken for IL studies. Most authors do not yet report water content, drying procedures (if any), or impurity levels.

Table 2 Water content of several water equilibrated (25 °C) and dried ILs[a]

Ionic liquid	Water equilibrated/ppm	Dried/ppm
$[C_4mim][Cl]$	Miscible	2200
$[C_4mim][I]$	Miscible	1870
$[C_4mim][BF_4]$	Miscible	4530
$[C_4mim][PF_6]$	11700	590
$[C_4mim][Tf_2N]$	3280	474
$[C_6mim][Cl]$	Miscible	1130
$[C_6mim][PF_6]$	8837	472
$[C_8mim][Cl]$	Miscible	890
$[C_8mim][PF_6]$	6666	388

[a] Water equilibrated refers to RTILs that have been stored in contact with water. Dried RTILs are water equilibrated RTILs that have been dried at 70 °C for 4 h on a vacuum line.

Melting point and glass transition

The solid–liquid phase transition of some of the current RTILs has been examined by DSC and the results are summarized in Tables 3 and 4. This behavior is relatively complex, as shown in Fig. 2. The DSC trace (exothermic up) shown in Fig. 2 is the heating curve for $[C_8mim][PF_6]$ where the glass transition is observed around −75 °C and the large peak at 0 °C can be attributed to the melting point of water. The broad exothermic transition between −25 and 0 °C may be due to the crystallization of water molecules or a simple reorganization of the water molecules prior to melting. Typically, the material in the solid crystalline state will exhibit a glass transition temperature on heating from low temperatures and may or may not be followed by a melting transiton (fusion) on further heating.

In our analyses, we observed melting points for only a few ILs. For the other samples, it is postulated that after passing through the glass transition temperature, the cations and anions must reorganize before a melting point will be observed. In the PF_6^- series, we did not observe melting points for $[C_6mim]^+$ or $[C_8mim]^+$, although the $[C_{10}mim]^+$ derivative melts slightly above room temperature.[17] Our analyses show a trend that has also been observed by Holbrey and Seddon.[23] These results and the crystal structure of $[C_{10}$ and $C_{12}mim][PF_6]$[17,44] suggest that

Table 3 Melting point data for several ILs

Ionic liquid	Melting point/°C (water equilibrated)	Melting point/°C (dried)	Lit. ref.
$[C_4mim][Cl]$		41	
$[C_4mim][I]$		−72	
$[C_4mim][PF_6]$	4	10	
$[C_4mim][Tf_2N]$	−25		
$[C_1mim][AlCl_4]$		125	45
$[C_2mim][AlCl_4]$		84	45
$[C_3mim][AlCl_4]$		60	45
$[C_4mim][AlCl_4]$		65	45
$[C_4C_4im][AlCl_4]$		55	45
$[C_2mim][NO_3]$		38	47
$[C_2mim][NO_2]$		55	47
$[C_2mim][CH_3CO_2]$		45	47
$[C_2mim][PF_6]$		58–60	47
$[C_2mim][TfO]$		9	34
$[C_2mim][NfO]$		28	34
$[C_2mim][Tf_2N]$		4	34
$[C_2mim][TA]$		14	34
$[C_3mim][PF_6]$		40	22
$[i\text{-}C_3mim][PF_6]$		102	22
$[C_4mim][BF_4]$		−81	36
$[C_6mim][PF_6]$		−61	36

Table 4 Glass transition temperatures of several ILs

Ionic liquid	T_g/°C (water equilibrated)	T_g/°C (dried)	Lit. ref.
$[C_4mim][BF_4]$		−97	
$[C_4mim][PF_6]$	−83	−80	
$[C_4mim][Tf_2N]$	−102	−104	
$[C_6mim][Cl]$		−75	
$[C_6mim][PF_6]$	−75	−78	
$[C_8mim][Cl]$		−87	
$[C_8mim][PF_6]$	−75	−82	
$[C_4mim][BF_4]$		−81	36
$[C_4mim][PF_6]$		−61	36
$[C_2mim][Tf_2N]$		−98	22
$[C_2mim][N(CF_2CF_3)_2]$		−85	22

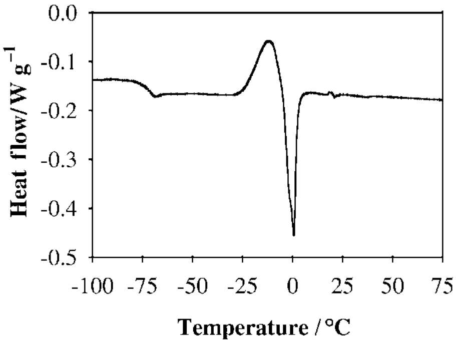


Fig. 2 Differential scanning calorimetry trace for water-equilibrated $[C_8mim][PF_6]$ (exothermic up).

as the alkyl chain length increases, inter-chain hydrophobic packing affects and the formation of bilayer-type structures result in an increase in melting points for salts of $[C_nmim]^+$ with $n > 8$.

Ngo *et al.* have examined the properties of a series of imidazolium ILs and indicate that the melting points decrease with the larger more asymmetrical substituted cations.[22] ILs containing the nonaflate (NfO) anion ($CF_3CF_2CF_2CF_2SO_3^-$) were reported to melt closer to room temperature. The structure of both the cations and the anions has an obvious effect, for example, in the series of cations with $AlCl_4^-$ where smaller and more symmetrical cations result in higher melting points than ILs composed of unsymmetrical or larger cations.[45] Increased branching of the alkyl group results in melting points higher than the linear analogs. Appending an isopropyl group instead of an *n*-propyl group increases the melting point by 82 °C (Table 3).[22] Hagiwara and Ito[46] and Bonhôte *et al.*[34] have indicated that there is not an overall correlation between the composition of the IL and its melting point.

Explaining the anion effect is more difficult, owing to the presence of water and its interactions with the cation and anion. For ILs containing structurally similar anions such as triflate (TfO^-) and Tf_2N^-, the lower melting point of the Tf_2N^- salt (Table 3) could be attributed to electron delocalization and the anion's inability to hydrogen bond.[34] This idea is substantiated by comparing the melting points for two similar cations, one containing a fluorinated methyl group, in combination with the TfO^- anion. The fluorines act to distort the electron density on the imidazolium ring and promote hydrogen bonding and a corresponding 50 °C difference in the melting points between the two ILs.[34] In a similar manner, differences between $[C_2mim][CF_3CO_2]$ and $[C_2mim][CH_3CO_2]$, besides the trifluoroacetate (TA) moiety having a melting point 31 °C lower than $CH_3CO_2^-$, can undoubtedly be attributed to the presence of fluorine atoms on that anion and their interaction with other anions and the cation.[34,47] The melting point for $[C_2mim][NO_2]$ is 17 °C higher than that for $[C_2mim][NO_3]$, suggesting that anion structure also contributes to the thermal properties.[47] The combination of imidazolium cations and carborane anions has also been recently explored by Larson *et al.*[48] to determine the factors that influence the melting points.

Supercooling, or glass formation, is a common characteristic associated with many, but not all, of the imidazolium ILs.[22,34,44,46,49] Literature reports indicate that dialkylimidazolium cations combined with Tf_2N^-, TA^-, and heptafluorobutanoates (HB) are generally liquid up to −30 to −50 °C, but become increasingly viscous and turn finally into glasses without the observation of a melting point.[34] The ILs examined here exhibited glass transition temperatures between −104 and −75 °C, a slightly wider range than what is reported in the literature.[22,49] Tf_2N^- and BF_4^- anions produce the lowest glass transition temperatures and those for Cl^- and PF_6^- are similar.

Thermal stability

The RTILs under study here have no distinguishable vapor pressure and, as a result, the first thermal event on heating of the ILs is thermal decomposition. In general, most ILs have a high thermal stability, often beginning to decompose around 400 °C with minimal vapor pressure below their decomposition temperature, as determined by thermal gravimetric analyses. Recent reports have described the TGA of imidazolium salts and noted that the thermal decomposition is heavily dependent on the salt structure and, for certain samples, the type of sample pan (*i.e.*, aluminium or alumina) used in the analysis.[22] Literature reports indicate that experiments performed under N_2 or air produce the same results.[34]

Thermal stability data are shown in Table 5. The onset of thermal decomposition temperatures are similar for the different cations but appear to decrease as the anion hydrophilicity increases. In general it also appears that drying improves the thermal stability of this class of ILs, although the results for $[C_4mim][PF_6]$ appear to be anomalous and, as yet, unexplained. The role of water in either situation, and the effect on ILs, has yet to be determined.

Table 5 Thermal decomposition temperatures of several ILs

Ionic liquid	Temp. onset for decomposition/°C (water equilibrated)	Temp. onset for decomposition/°C (dried)	Lit. ref.
$[C_4mim][Cl]$		254	
$[C_4mim][I]$		265	
$[C_4mim][BF_4]$		403	
$[C_4mim][PF_6]$	360	349	
$[C_4mim][Tf_2N]$	394	439	
$[C_6mim][Cl]$		253	
$[C_6mim][PF_6]$	390	417	
$[C_8mim][Cl]$		243	
$[C_8mim][PF_6]$	374	376	
$[C_2mim][Cl]$		285	22
$[C_2mim][I]$		303	22
$[C_2mim][PF_6]$		375	22
$[C_2mim][BF_4]$		412	22
$[C_2mim][Tf_2N]$		455	22
$[C_2mim][Tf_2N]$		~440	34
$[C_2mim][CF_3COO]$		~150	34
$[C_2mim][CF_3SO_3]$		~440	34
$[C_3mim][Cl]$		282	22
$[C_3mim][PF_6]$		335	22
$[C_3mim][Tf_2N]$		452	22
$[C_4mim][BF_4]$		360	23
$[C_{18}mim][BF_4]$		360	23

Bonhôte *et al.* found that $[C_2mim][CF_3SO_3]$ and $[C_2mim][Tf_2N]$ were stable up to 400 °C and decomposed rapidly between 440 and 480 °C. On the other hand, $[C_2mim][TA]$ was only stable to 150 °C and then decomposed rather slowly to 250 °C.[34] Larger fluorinated organic anions (*e.g.*, $N(SO_2CF_2CF_2CF_2CF_3)_2^-$) combined with $[C_2mim]^+$ produced similarly stable ILs, beginning to decompose above 400 °C.[49] Substituting the ring hydrogens with methyl groups, especially the C2 hydrogen, added to the stability of the cation[46] and one proposed decomposition mechanism involves proton abstraction to produce both volatile acids from the anion and carbene derivatives of the cation.

Halide anions dramatically reduce the thermal stability with the onset of decomposition occurring at least 100 °C below the corresponding ILs with non-halide anions.[22] Relative anion stabilities have been suggested as $PF_6^- > Tf_2N^- \sim BF_4^- >$ halides,[22] concurrent with the results in Table 5. Increasing the cation size from $[C_4mim]^+$ to $[C_8mim]^+$ doesn't appear to have a large effect, since even more dramatic changes in cation size ($[C_4mim]^+$ to $[C_{18}mim]^+$) produced the same results.[23]

Viscosity

Viscosity data for a number of these RTILs are presented in Table 6. Hagiwara and Ito have determined that the viscosities of imidazolium ILs with fluorinated anions are much greater than that of water and, as can be expected, the longer alkyl substituents produce more viscous RTILs.[46] In our results, the viscosities in this type of RTILs are two or more orders of magnitude greater than that found for most traditional organic liquids (solvents) and are more comparable to a typical oil.[50] At a particular temperature, they seem to be actually more viscous than soybean oil but somewhat less viscous than glycerin.[50] These viscosities are also higher than those found for alkylammonium nitrate and thiocyanate salts by Poole *et al.*[24] and tetrachloroaluminates.[47]

Changing the experimental conditions allows further exploration of the nature of IL behavior. An increase in temperature shows that the viscosity increases in a non-Arrhenius fashion for the $[C_n\text{mim}][PF_6]$ ILs, as shown in Fig. 3. Other studies have investigated how the shear rate affects the viscosity.[51] Thus, ILs can be classified in terms of being a Newtonian fluid whose viscosity remains constant with increasing shear rates, or a thixotropic fluid whose viscosity decreases as the shear rate increases. For $[C_n\text{mim}][BF_4]$ (n = 4, 6, 8), the shear rate produced no difference in the viscosity.[51] Longer alkyl chains, (*e.g.*, $[C_{12}\text{mim}][BF_4]$) show non-Newtonian behavior, although temperature has a significant effect on the results.[51]

IL impurities have a significant affect on viscosity as well as other properties. Another report has measured the effect of water, sodium chloride, and organic solvents on IL physical properties.[52] For example, $[C_4\text{mim}][BF_4]$ with 0.01 molal Cl^- has a viscosity of 154 (mPa s^{-1}) and an increase to 0.5 molal Cl^- increases the viscosity to 201 (mPa s^{-1}).[52] This aspect raises the important point that, in consideration of ILs for use in processes where it would be in contact with another phase, cross-contamination of the ILs may drastically affect the physical properties.

Table 6 Viscosity data (25 °C, unless indicated otherwise) for several ILs

Ionic liquid	Viscosity/cP (water equilibrated)	Viscosity/cP (dried)	Lit. ref.
$[C_4\text{mim}][I]$		1110	
$[C_4\text{mim}][BF_4]$		219	
$[C_4\text{mim}][PF_6]$	397	450	
$[C_4\text{mim}][Tf_2N]$	27	69	
$[C_6\text{mim}][Cl]$		716	
$[C_6\text{mim}][PF_6]$	452	585	
$[C_8\text{mim}][Cl]$		337	
$[C_8\text{mim}][PF_6]$	506	682	
$[C_4\text{mim}][Tf_2N]$		52	34
$[C_4\text{mim}][CF_3CO_2]$		73	34
$[C_4\text{mim}][CF_3SO_3]$		90	34
$[C_4\text{mim}][CF_3CF_2CF_2CF_2SO_3]$		373	34
$[C_2\text{mim}][BF_4]$		43	49
$[C_2\text{mim}][Tf_2N]$		28	49
$[C_4\text{mim}][BF_4]$		233	36
$[C_4\text{mim}][BF_4]$ (20 °C)		154	52
$[C_2\text{mim}][BF_4]$ (20 °C)		66.5	51
$[C_2\text{mim}][BF_4]$ (30 °C)		43	51
$[C_4\text{mim}][BF_4]$ (20 °C)		154	51
$[C_4\text{mim}][BF_4]$ (30 °C)		91.4	51
$[C_6\text{mim}][BF_4]$ (20 °C)		314	51
$[C_6\text{mim}][BF_4]$ (30 °C)		177	51
$[C_4\text{mim}][PF_6]$ (20 °C)		371	51
$[C_4\text{mim}][PF_6]$ (30 °C)		204	51
$[C_6\text{mim}][PF_6]$ (20 °C)		680	51
$[C_6\text{mim}][PF_6]$ (30 °C)		363	51
$[C_8\text{mim}][PF_6]$ (20 °C)		866	51
$[C_8\text{mim}][PF_6]$ (30 °C)		452	51
$[C_4\text{mim}][PF_6]$		312	36

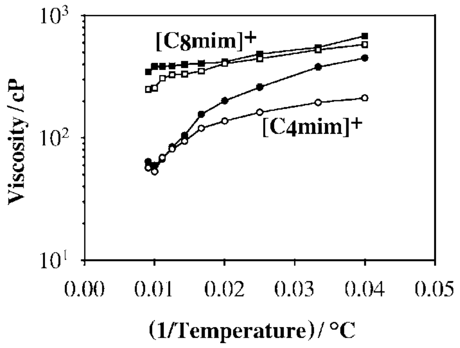


Fig. 3 Viscosity of a series of ILs as a function of increasing temperature: dried samples (filled symbols), water equilabrated samples (open symbols).

Such viscosities, as observed here and in the literature, will critically affect rates of mass transfer and power requirements for mixing in liquid reaction systems. The viscosities, especially for PF_6^- ILs, are substantially higher than the majority of those found by Bonhôte *et al.*, for a similar series of ILs,[34] but substantially lower than those reported for a series of tetraalkylammonium sulfonates.[53] That they are not in error is suggested by the close correspondence of our data for $[C_4\text{mim}][Tf_2N]$ (69 cP) and that given by Bonhôte *et al.* of 55 cP.[34] The data for $[C_4\text{mim}][PF_6]$ and $[C_2\text{mim}][CF_3CF_2CF_2CF_2SO_3]$ liquid organic salts indicate viscosities more comparable to those found here.

An increase in the viscosity of the various anion/cation combinations was attributed to an increase in van der Waals forces over hydrogen bonding.[34] Such an explanation might also be applicable to our own results, however, hydrogen bonding between cationic protons and anionic halides has been noted in the crystalline state from X-ray diffraction studies[17] and may represent an additional factor. In addition, the increased symmetry of the inorganic anions (*e.g.*, PF_6^- or BF_4^-) compared to the organic anion (Tf_2N^-) may play an important role. The results of Table 6 seems to indicate that the geometry and molar mass of the anions have a strong influence on the viscosity of this class of IL since $[C_4\text{mim}]^+$ combined with either PF_6^- or Tf_2N^- produces ILs with significantly different viscosities. These results suggest a complex relationship where the importance of cation–anion interactions as well as the presence of water cannot be overlooked.[52]

Surface tension

Surface tension data for several RTILs have been obtained and these are shown in Table 7. In general these liquid/air surface tension values are somewhat higher than for conventional solvents (*e.g.*, hexane: 18 dyn cm^{-1}, toluene: 32 dyn cm^{-1}), but not so high as water (73 dyn cm^{-1})[50] which will tend to mitigate against liquid–liquid phase mass transfer but at the same time promote more rapid phase disengagement.

Table 7 Surface tension data (25 °C) for several ILs

Ionic liquid	Surface tension/dyn cm^{-1} (water equilibrated)	Surface tension/dyn cm^{-1} (dried)
$[C_4\text{mim}][I]$		54.7
$[C_4\text{mim}][BF_4]$		46.6
$[C_4\text{mim}][PF_6]$	49.8	48.8
$[C_4\text{mim}][Tf_2N]$	36.8	37.5
$[C_6\text{mim}][Cl]$		42.5
$[C_6\text{mim}][PF_6]$	36.8	43.4
$[C_8\text{mim}][Cl]$		33.8
$[C_8\text{mim}][PF_6]$	34.2	36.5

Density

It may be readily observed from the density data presented in Table 8, that the molar mass of the anion significantly determines the overall density found for each RTIL. Using halogenated carborane anions, the density can be as high as 2.151 g cm^{-3}.[48] Adding CH$_2$ groups to the alkyl chain on the [C$_n$mim]$^+$ cation decreases the density since CH$_2$ is less dense than an imidazolium ring. Dependence of the density on the carbon number of the anion (in this case) was also found for a series of alkylammonium sulfonate liquid organic salts.[54]

In our studies, the simple halide salts have significantly lower densities than the PF$_6^-$ RTIL, and these lower densities are comparable to other solvents (*e.g.*, [C$_8$mim][Cl] is similar to water, [C$_6$mim][Cl] is similar to dioxane[50]). The contribution of the larger hydrophobic anions is significant for the water immiscible ILs and the densities found are comparable to carbon disulfide or glycerin.[50] Such densities would be advantageous to the phase separation of immiscible liquids mixtures but disadvantageous to the power requirements of mixing. However, for both hydrophobic and hydrophilic ILs, an increase in the water content causes the density to decrease and approach that of water, as shown in Table 8.

Table 8 Densities (25 °C) of several ILs

Ionic liquid	Density/g mL^{-1} (water equilibrated)	Density/g mL^{-1} (dried)	Lit. ref.
[C$_4$mim][Cl]		1.08	
[C$_4$mim][I]		1.44	
[C$_4$mim][BF$_4$]		1.12	
[C$_4$mim][PF$_6$]	1.35	1.36	
[C$_4$mim][Tf$_2$N}	1.39	1.43	
[C$_6$mim][Cl]		1.03	
[C$_6$mim][PF$_6$]	1.24	1.29	
[C$_8$mim][Cl]		1.00	
[C$_8$mim][PF$_6$]	1.16	1.22	
[C$_4$mim][Tf$_2$N]		1.429	34
[C$_4$mim][CF$_3$CO$_2$]		1.209	34
[C$_4$mim][CF$_3$SO$_3$]		1.290	34
[C$_4$mim][BF$_4$]		1.17	36
[C$_4$mim][PF$_6$]		1.37	36

Refractive index

The refractive index data are shown in Table 9. The refractive index is related to the polarizability/dipolarity of the medium and the excess molar refraction is used in the least squares energy relationships (LSERs) of Abraham *et al.* as a predictor of solute distribution.[55–57] These results are quite comparable with values for typical organic solvents and are similar to the values reported for the alkylammonium IL salts reported by Shetty *et al.*[25]

Table 9 Refractive index (25 °C) for several ILs

Ionic liquid	Refractive index (dried)	Lit. ref.
[C$_4$mim][I]	1.572	
[C$_4$mim][PF$_6$]	1.409	
[C$_6$mim][Cl]	1.515	
[C$_8$mim][Cl]	1.505	
[C$_8$mim][PF$_6$]	1.423	
[C$_4$mim][Tf$_2$N]	1.4271	34

Organic solute partitioning

We have previously demonstrated[16] that organic solute partitioning from water to [C$_4$mim][PF$_6$] in general follows the log *P* (1-octanol/water) values for the solutes. Fig. 4 illustrates the trend in partitioning is very similar for [C$_6$mim][PF$_6$] and the actual distribution ratios vary only slightly, indicating that contacting [C$_4$mim][PF$_6$] or [C$_6$mim][PF$_6$] with water produces only small differences in the water content for the IL phase.

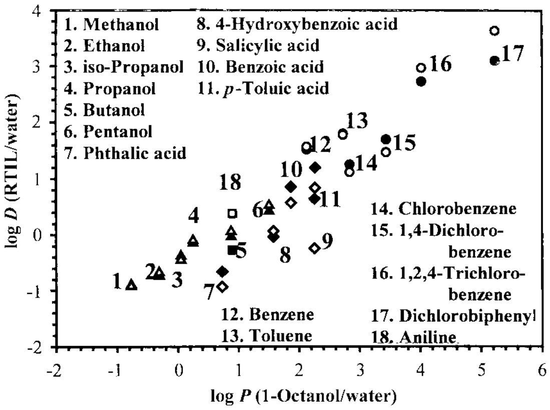


Fig. 4 Comparison of distribution ratios of selected organic molecules between [C$_4$mim][PF$_6$]/water (filled symbols) or [C$_6$mim][PF$_6$]/water (open symbols) with log *P* (1-octanol/water) data.

There are few reports concerning the miscibility with other solvents. Certain RTILs are reported to be miscible to 0.66 mole fraction with benzene although solutes with larger dipole moments are more soluble.[12] The contact of supercritical CO$_2$ (sc-CO$_2$) with [C$_4$mim][PF$_6$] represents a unique situation, as observed by Blanchard *et al.*,[10] because sc-CO$_2$ is readily soluble in the RTIL, although very little of that RTIL is miscible with the supercritical fluid. Other studies of sc-CO$_2$ in ILs have used attenuated total reflectance infrared spectroscopy to determine the anion effect in the Lewis acid–base interactions with CO$_2$.[11]

Studying the solute partitioning in IL systems unearths some inevitable comparisons to the partitioning behavior of the same solute in more traditional liquid/liquid separations systems. Indeed, ILs can be considered a novel class of solvents, but, in light of the profusion of traditional organic solvents available with their associated variations in solvent properties, to what class of solvents can ILs be likened in terms of their solvating power, *etc.*? Bonhôte *et al.* used pyrene and pyrenecarboxaldehyde to study the fluorescence of those probe molecules in ILs and, also, the phosphorescence of bromonaphthalene to investigate the microenvironments of ILs.[34] Other work has used Nile Red[58] to report on the solvatochromatic response for a variety of ILs and, separately, fluorescence probes to study imidazolium and pyridinium ILs.[59] In a subsequent paper, we report the use of several different probe molecules to study the solvatochromatic response of both hydrophobic and hydrophilic ILs leading to their classification in terms of more familiar solvents. This work also delves into the use of organic solute partitioning and LSERs, to model the partitioning of solutes in IL systems.[60]

Conclusions

For the set of [C$_n$mim]$^+$ RTILs examined here, the resulting physical properties show that anion identity is of foremost importance. Our observations show how sensitive the resulting properties are towards the water miscibility and content, sometimes shifting the results an order of magnitude. Water content and hydrophobicity are also connected to changes in cation substitution and can be a significant factor when considering the applications of a particular IL. As a result, simple variations in cation and anion structure and overall ionic composition illustrate the ease in which physical properties of a class of ILs can be modified to produce a wide range of solvent media. A recent publication[61] has detailed a series of 58 ILs (38 represent new ILs) based on the imidazolium cation and, in the overall picture, illustrates the vast number of ILs available and the daunting task of their characterization. The report also includes the first published toxicity data (LD_{50}) for 3-hexyloxymethyl-1-methylimidazolium BF_4.[61]

In light of how ILs are being proposed for use where traditional organic solvents have been the norm, it is interesting how the results reported here indicate several properties of ILs are quite different from traditional organic solvents. Most notable for the RTILs is the lack of significant vapor pressure despite their ability to solubilize materials. The ionic nature present in these neoteric solvents presents both a promising opportunity and a challenge; to explore the properties and applications of ILs, and to better understand how the ionic environment sustains the ILs while producing such novel properties.

Experimental

All aqueous solutions were prepared with deionized water that was purified with a Barnsted deionization system (Dubuque, IA) and polished to 18.3 MΩ cm. All salt and acid solutions were prepared as molar concentrations by transferring a known amount of material to a volumetric flask and diluting to the specified volume with deionized water. When needed, pH adjustments of the aqueous phase were made using H_2SO_4 or NaOH.

HPF_6 was supplied by Ozark Mahoning (Tulsa, OK) and was used as received. $LiN(CF_3SO_2)_2$ was supplied by 3M (Minneapolis, MN) and used as received. All other chemicals were of reagent grade, obtained from Aldrich (Milwaukee, WI) and used without further purification. Organic molecule partitioning was done with ^{14}C labeled solutes obtained from Sigma (St. Louis, MO).

Synthesis of ionic liquids

[C$_4$mim][Cl]. Equal molar amounts of chlorobutane and 1-methylimidazole were added to a round-bottomed flask fitted with a reflux condenser for 24–72 h at 70 °C with stirring until two phases formed. The top phase, containing unreacted starting material, was decanted and ethyl acetate (a volume approximately equal to half that of the bottom phase) was added with thorough mixing. The ethyl acetate was decanted followed by the addition of fresh ethyl acetate and this step was repeated twice. Washing with ethyl acetate should suffice to remove any unreacted material from the bottom phase. After the third decanting of ethyl acetate, any remaining ethyl acetate was removed by heating the bottom phase to 70 °C and stirring while on a vacuum line. The product, [C$_4$mim][Cl], is slightly yellow and may be crystalline at room temperature, depending on the amount of water present in that phase.

The H NMR spectrum for [C$_4$mim][Cl] (D_2O, ppm) consist of the following peaks: δ 0.95 (t), 1.38 (sextet), 1.80, (q), 3.70 (s), 4.00 (s), 4.30 (t), 7.00 (s), 7.15 (s), 7.55 (s). ^{13}C NMR results (ppm) include: δ 15.72, 34.21, 36.04, 38.69, 52.14, 124.16, 126.39 and 141.16.

[C$_4$mim][PF$_6$]. [C$_4$mim][Cl] was transferred to a 2 L plastic container (lined with a perfluorinated material) followed by the addition of 500 mL deionized water. An aqueous solution of 60% HPF_6 in a 1.1 : 1 molar ratio was added. **CAUTION**: the addition of HPF_6 should be done slowly to minimize the amount of heat generated. As HPF_6 was added, two phases formed, where [C$_4$mim][PF$_6$] was the bottom phase and HCl was the upper phase. The upper phase was decanted and 500 mL of water was added followed by vigorous shaking and mixing. After the mixture settles, the upper aqueous phase was decanted and more deionized water was again added. This procedure was repeated until the pH of the upper phase was *ca.* 7.

The [C$_4$mim][PF$_6$] was stored in contact with water and is referred to as water-equilibrated or 'wet'. An aliquot of the wet [C$_4$mim][PF$_6$] was dried at 70 °C on a vacuum line for 4 h to produce the 'dried' version of the IL. (The IL was not extensively dried because, realistically, the results would not be practical towards our intended applications). In addition, despite being dried for several hours, when the IL is removed from the vacuum line it will readily reabsorb water from air since our analyses and characterization experiments were not carried out in a glove box.

Analysis of [C$_4$mim][PF$_6$] included H (360.13 MHz) and ^{19}F (470.56 MHz) NMR. Each H NMR spectrum contained peaks corresponding to the [C$_n$mim]$^+$ cation and indicated no residual reactants. The chemical shifts (ppm, neat sample) for the H NMR of [C$_4$mim][PF$_6$] appear as follows: δ 0.72 (t), 1.15 (sextet), 1.68 (qnt), 2.25 (s, br), 3.73 (s), 4.05 (t), 7.22 (s), 7.30 (s) and 8.26 (s). The ^{19}F NMR spectra consist of two peaks, one at δ −74 and the other at δ −72.5, corresponding to the splitting of ^{19}F ($I = \frac{1}{2}$) by ^{31}P ($I = \frac{1}{2}$). ^{13}C NMR (neat sample, ppm) shows peaks at δ 17.72, 24.03, 36.52, 40.58, 54.41, 127.16, 128.49 and 141.27. The H NMR analyses were performed on a Bruker AM 360 instrument (Houston, TX) while ^{19}F NMR analyses used a Bruker AM 500 instrument (Houston, TX).

[C$_4$mim][BF$_4$]. [C$_4$mim][Cl] was transferred to a 2 L plastic container (lined with a perfluorinated material) followed by the addition of aqueous HBF_4 (40%) at a 1.1 : 1 molar ratio. [C$_4$mim][BF$_4$] was separated from the HCl by extraction into a volume of methylene chloride approximately equal to the initial amount of [C$_4$mim][Cl]. The addition of methylene chloride was followed by thorough mixing and transfer of the solution to a separatory funnel where the organic phase was the upper phase. The [C$_4$mim][BF$_4$–methylene chloride mixture was put in a round-bottomed flask to rotovap at 95 °C under a vacuum to remove any residual methylene chloride.

The H NMR spectrum (ppm, acetone-d$_6$, dried) for [C$_4$mim][BF$_4$] showed peak locations remained essentially the same as those for [C$_4$mim][Cl], although the ^{19}F NMR spectra has a singlet at δ −152.,86. The ^{13}C NMR spectrum (*d*-acetone, ppm, dried) contains peaks at δ 13.12, 19.30, 31.94, 35.90, 54.45, 122.56, 123.84 and 136.67.

[C$_4$mim][I]. This synthesis followed the same procedure as for [C$_4$mim][Cl] described above, although iodobutane was used instead of chlorobutane. [C$_4$mim][I] was slightly darker and the yield was approximately 70%. All other steps remain the same. The H NMR spectrum (ppm, dried, neat sample) for [C$_4$mim][I] resulted in peak locations similar to those for [C$_4$mim][Cl].

[C$_4$mim][Tf$_2$N]. Approximately 100 g of [C$_4$mim][Cl] was transferred to a 250 mL plastic bottle and a 1.1 : 1 molar ratio of Li(Tf$_2$N) was added, followed by 50 mL of deionized water. After mixing, two phases formed where the bottom phase was [C$_4$mim][Tf$_2$N] and the top phase was aqueous LiCl. Both phases were colorless. After decanting the top phase, 50 mL of fresh deionized water was added and the solution was thoroughly mixed. This was repeated twice.

Analysis of [C$_4$mim][Tf$_2$N] by H NMR (neat sample, ppm) produced a spectrum similar to that for [C$_4$mim][Cl]. The ^{13}C NMR spectrum is also similar to [C$_4$mim][Cl] with the addition of peaks at δ 115.56 and 122.66.

[C$_6$mim][Cl]. The same procedure was used as indicated for [C$_4$mim][Cl] with the exception of the use of chlorohexane instead of chlorobutane. The product is a tan liquid that is markedly more colored than [C_4mim][Cl] or [C_8mim][Cl]. The yield is approximately 80%. Analysis of [C_6mim][Cl] by H NMR (neat sample, dried, ppm) resulting in a spectrum similar to that for [C_4mim][Cl] with the addition of a multiplet of peaks at δ 2.05.

[C_6mim][PF_6]. The same procedure was used as for [C_4mim][PF_6]. Here, the tan color associated with [C_6mim][Cl] was carried through in this step and is not removed by repeated washing. Analysis of [C_6mim][PF_6] by H NMR (neat sample, dried, ppm) gave a spectrum identical to that for [C_6mim][Cl] with the addition of a small, broad peak at δ 2.30. The impurity contributing to the tan color was not observed by NMR. The F NMR spectrum was very similar to that for [C_4mim][PF_6] with no additional peaks.

[C_8mim][Cl]. The same procedure was used as for [C_4mim][Cl] with the substitution of chlorooctane for chlorobutane. The product is a colorless liquid with a yield of *ca.* 80%. Analysis of [C_8mim][Cl] by H NMR (neat sample, dried, ppm) resulted in a spectrum containing the following peaks: δ 0.67 (t), 1.08 (m), 1.70 (m), 3.75 (s), 4.10 (t), 4.68 (s), 5.27 (s), 7.35 (d) and 8.40 (d). The ^{13}C NMR (neat, dried, ppm) spectrum shows the following peak locations: δ 13.28, 21.96, 25.28, 29.51, 30.68, 35.37, 49.35, 53.86, 119.55, 122.06, 123.41 and 136.04.

[C_8mim][PF_6]. The same procedure was used as for [C_4mim][PF_6]. The product is a colorless liquid. Analysis of [C_8mim][PF_6] by H NMR (neat sample, dried, ppm) gave spectra containing no extraneous peaks that were not assigned to the [C_8mim][Cl] sample. The F NMR (neat sample, dried, ppm) showed the same peaks observed for both [C_4mim][PF_6] and [C_6mim][PF_6].

Water content

The water content of each RTIL was determined using a volumetric Aquastar Karl Fischer titrator (EM Science, Gibbstown, NJ) with Composite 5 solution as the titrant and anhydrous methanol as the solvent. Each sample was at least 1 g and duplicate measurements were performed on each sample with results agreeing to within 5%.

Melting point and glass transition temperature

Melting point and glass transition temperatures were determined by differential scanning calorimetry using a TA Instruments (New Castle, DE) model 2920 differential scanning calorimeter. Each sample was approximately 10 mg and analyzed in a hermetically sealed aluminium pan. For each experiment, an empty hermetically sealed pan was referenced as the blank. A ramp temperature of 10 °C min^{-1} was employed over the temperature range of -150 to 100 °C. Temperature calibration was performed on a sample of indium.

Decomposition temperatures

The range of thermal decomposition temperatures for each IL was determined by thermogravimetric analysis using a TA Instruments (New Castle, DE) model 2950 thermogravimetric analyzer. Each sample was analyzed in a platinum pan with nitrogen as the purge gas. In each experiment, the temperature was linearly increased at 10 °C min^{-1} over a temperature window of 30 to 600 °C.

Viscosity

The viscosity of each RTIL was measured with a Cole-Parmer (Vernon Hills, IL) 98936 series viscometer. For each analysis, an 8 mL sample was used and the measurements were performed in duplicate. The temperature of the sample was maintained to ±0.1 °C *via* an external temperature controller. A correction factor for each of the experimentally determined values was determined by measuring the viscosity of a Cannon (State College, PA) certified viscosity standard (S200). Each sample was analyzed in duplicate and the results agree to within 10 cP.

Surface tension

The surface tension of each RTIL was measured with a Fisher brand manual model 20 tensiometer with a 6 cm platinum–indium wire. A glass sample dish was used to hold the 40 mL sample volume used for each analysis. A correction factor for each measurement was determined by measuring the surface tension of DI water, dividing the result by its established value, and multiplying the results for the surface tension of RTILs by that value. All readings were taken at ambient temperature (25 ± 1 °C). Each sample was analyzed in triplicate and the average value is reported.

Density

The density of each RTIL was determined by gravimetric analysis. After calibrating a 1 mL pipet to dispense 1 g mL^{-1} of water, that pipette was used to transfer 1 mL of each RTIL to determine the mass of that volume of liquid. Each measurement was repeated 10 times and the average value is reported. All measurements were taken at room temperature (25 ± 1 °C).

Refractive index

All measurements were made with a ABBE Bausch and Lomb refractive index instrument. The instrument was calibrated by measuring the refractive index of deionized water. The sample holder was rinsed with 80% ethanol–water solution between each sample, dried with a paper towel and rinsed with the sample to be measured a minimum of two times. All measurements were made at 25 °C.

^{14}C-labelled solute partitioning

Liquid scintillation analyses were performed for analysis of ^{14}C-labelled organics using Ultima Gold scintillation cocktail (Packard Instrument, Downers Grove, IL) and a Packard Tri-Carb 1900 TR Liquid Scintillation Analyzer.

The organic solute distribution ratios were determined by mixing 1 mL of RTIL and 1 mL of an aqueous phase followed by vortexing (2 min) and centrifuging (2000 *g*, 2 min) to equilibrate the phases. Addition of the organic tracer (*ca.* 0.005 µCi, 5 µL) was followed by two intervals of vortexing (2 min) and centrifuing (2000 *g*, 2 min) to ensure that the phases were fully separated. Each tube was uncapped and 100 µL of each phase was removed for radiometric analysis. Since equal volumes of both phases were removed for analysis, the distribution ratio for the organic solutes was determined as in eqn. (1):

$$D = \frac{\text{Activity in the RTIL lower phase}}{\text{Activity in the aqueous upper phase}} \qquad (1)$$

Each experiment was carried out in duplicate and the results agreed to within 5%.

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A stereoselective route to 3-methyl-2-methylsulfanyl-5-ylidene-3,5-dihydroimidazol-4-one derivatives and precursor of Leucettamine B

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A range of aromatic aldehydes **8a-f** was tested in Knoevenagel reaction with 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one **7** and piperidine as catalyst using solvent-free conditions under microwave-mediated conditions. The results of these condensations were compared to classical procedure in methylene chloride. This efficient, simple and environmentally friendly methodology gave respectively and stereoselectively the (5*Z*)-5-arylidene-3,5-dihydroimidazol-4-ones **9a–e** in good yields (78–95%) and the precursor **9f** of Leucettamine B. Then, these solvent-less condition reactions have been also applied to cyclic ketones **10a–d**, acetone **12a** and actived ketones **12b**,**c**. The ^{1}H, ^{13}C NMR spectrum of some representative 5-ylidene-3,5-dihydroimidazol-4-ones are also reported.

Introduction

The imidazolone ring often appears as the core structure in many drug substances, covering a wide range of pharmacological activities.[1] Among this class of compounds, the 2-alkylthioimidazolones presents interesting biological activities. As examples, the (*S*)-glucosylated 5-arylideneimidazol-4-ones **I** (Fig. 1) exhibit properties as antiviral agents[2] and the alkylidene-imidazolones **II** substituted at C-2 with a [biphenyl-2-yl]tetrazole (BPT) group showed activities as angiotensine II receptor antagonists.[3] The 2-alkylthio imidazolones are also precursors for the synthesis of 2-amino imidazolones and a number of these derivatives display a wide range of biological activities including anticonvulsant[4] and protein kinase C[5] activities. Recently Roue and Bergmann[6] have reported the synthesis of Leucettamine B **III** using the thiohydantoïn route[7] (this 2-aminoimidazolone was previously isolated in 1993 from the marine sponge *Leucetta microraphis*[8] and showed an important role as mediator of inflammation[9]). Owing to the important place in pharmaceutical research occupied by the imidazolinone family, there are also several reports involving the solid phase synthesis.[10]

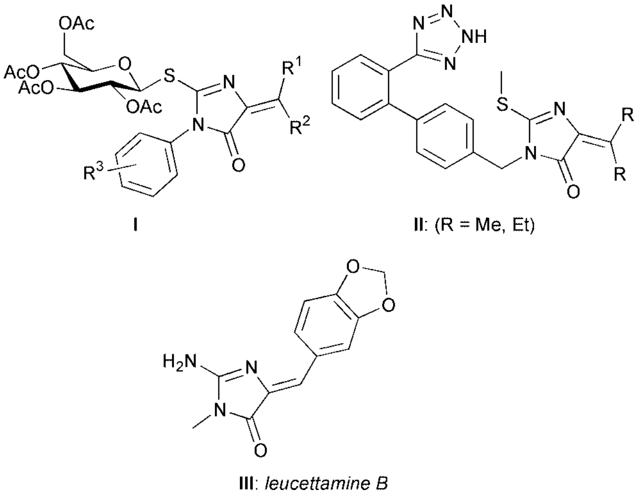

Fig. 1 Some imidazolone derivatives which present pharmacological activities.

Many processes associated with the pharmaceutical industry result in the production of large quantities of waste. From an environmental point of view, potent toxic waste should be minimized and, obviously, bulk wastes in chemical reactions are often organic solvents. Thus, the development of solvent-free organic synthesis[11] assisted by the use of focused microwave technology[12] has received much attention.

As part of research aimed at greener chemistry,[13] our priority was to develop a low-waste method for Knoevenagel reactions[14] from various aromatic aldehydes **8** and cyclic ketones **10** with 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one **7**. We describe here the synthesis of these new 4-arylidene-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-ones **9** using a solvent-free method assisted by focused microwave irradiations and have compared the results to classical procedure (methylene chloride as solvent).

Green Context

While alternative reaction media such as supercritical fluids can represent interesting and more environmentally benign solvents for many organic reactions it must often be true that the complete avoidance of a solvent is the most attractive option. Here some very efficient solventless reactions are described. Imidazolones are successfully synthesised *via* the Knoevenagel reaction using microwave conditions without solvent. The precursor to the inflammation mediator Leucettamine B is one of the molecules synthesised in this way. The methodology still offers some challenges however, since a volatile organic solvent is used to extract the product. *JHC*

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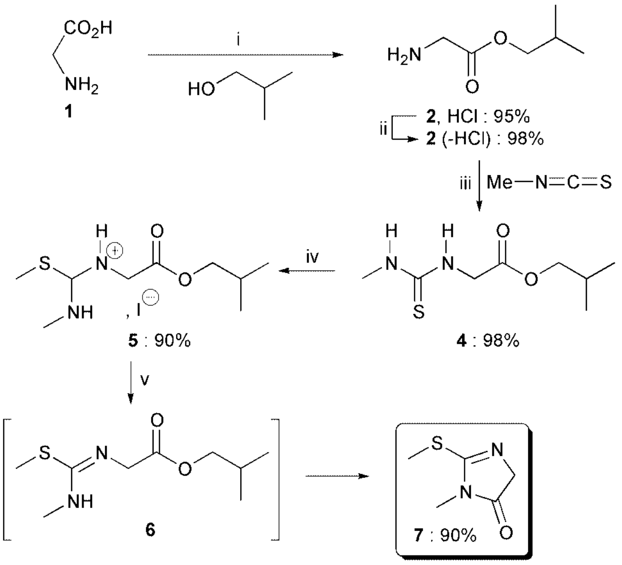
Results and discussion

Scheme 1 shows the route for the cheap preparation of 3-methyl-2-methylsulfanyl-3,4-dihydroimidazol-4-one **7** in large scale (up to 20 g) with an overall yield of 74% (five steps). The starting isobutyl aminoester hydrochloride **2** was prepared in 95% yield according to standard esterification from glycine and thionyl chloride, followed by neutralisation with saturated $NaHCO_3$ in methylene chloride to give **3**. The free and stable isobutyl aminoester[15] **3** was employed to minimize side reactions of both inter- and intra-molecular nature.[16] Then, reaction of **3** with methylisothiocyanate gave quantitatively the thiourea **4** which was converted to (*S*)-methyl isothiourea **5** (90%) after addition of methyl iodide. Ring closure was accomplished by addition of triethylamine to **5** in a refluxed mixture of solvent (Et_2O–CH_2Cl_2 2 : 1 v/v) and provided the expected 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one **7** in 90% yield after recrystallization from pentane *via* the intermediate **6** which could not be isolated.



Scheme 1 Preparation of 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one **7**. *Reagents and conditions*: i, $SOCl_2$ 1.1 equiv., 0 °C then 3 h at 70 °C; ii, sat. $NaHCO_3$, CH_2Cl_2, 25 °C, 3 h; iii, CH_2Cl_2, 0 °C then 4 h at 25 °C; iv, MeI 1.5 equiv., MeOH, heat, 1 h; v, Et_3N 1 equiv., Et_2O–CH_2Cl_2 (2 : 1), heat, 3 h, then recrystallization from pentane.

To prepare 5-arylidene-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-ones **9** (Scheme 2), we have developed and tested two experimental procedures.

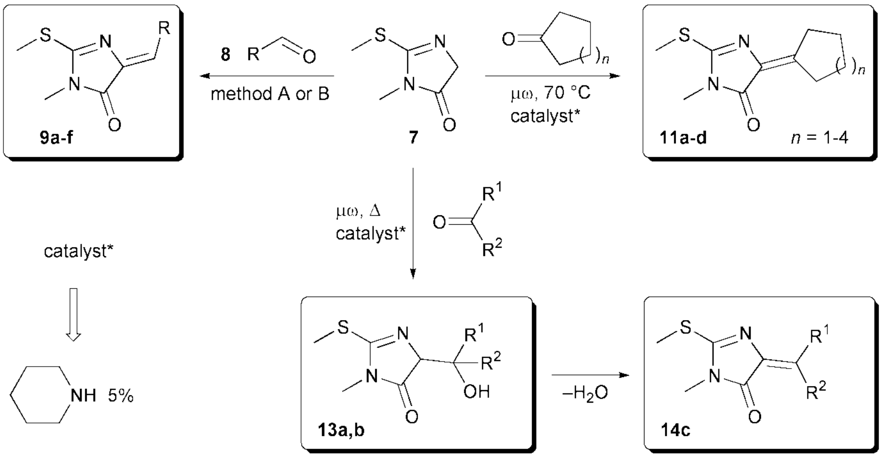
In method A, an equimolar mixture of freshly distilled aromatic aldehyde **8** and **7** with a catalytic amount of piperidine (5%) was refluxed in methylene chloride (15 mL) with vigorous magnetic stirring during the appropriate reaction time (Table 1). This reaction was monitored by thin layer chromatography with precoated plates of silica gel 60F 254 (Merck). Then, the solution was allowed to cool to room temperature, washed with water, dried over anhydrous $MgSO_4$. The filtrate was concentrated *in vacuo* to give the expected imidazolone **9**.

In method B, the base catalysed synthesis of 5-arylidene imidazolone **9** was easily achieved without solvent at 70–90 °C under focused microwave irradiations. It should be noted that the adequate reaction conditions were founded after several experiments (at various powers, temperatures and irradiation times). With the solvent-less conditions, the reaction was readily monitored by ^1H NMR spectroscopy. The desired 5-arylidene imidazolones **9** were then extracted from the microwave reactor by addition of methylene chloride and the organic solution was treated as previously described in method A.

The results summarized in Table 1, shows that the 5-aryliden-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-ones **9a–f** were obtained in yields ranging from 71 to 90% for method A while for method B the reactions proceeded cleanly in high yields (78–95%), with no evidence of decomposition of the desired imidazolone **9**. Comparison of the two methods shows an acceleration of the reaction rate and yield enhancements for the synthesis of compounds **9** using the method B. The high reactivity of **7** under solvent-free conditions may be attributed to the higher concentration of neat **7** with aromatic aldehyde **8** than in solution.

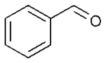
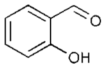
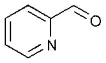
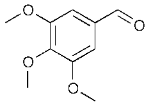
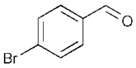
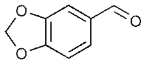
The structural assignment of compounds **9a–f** is based on spectroscopic data (^1H, ^{13}C NMR, mass spectrometry). In all cases, the condensation reactions were stereospecific and the (5*Z*)-stereochemistry of compounds **9** was based on the shielding effect of the carbonyl group on the olefinic proton H-5.[17] (**9a–f**: δ_{H-5} 6.84–6.95). It should be noted that condensation of piperonal **8f** on **7** at 70 °C (method B) gave stereoselectively the interesting product **9f** as a precursor of Leucettamine B (**9f** is converted into Leucettamine B after displacement[18] of the MeS group with an amine) in 92% yield and short reaction time (20 min).

In order to define the ability of the 2-methyl-3-methylsulfanyl-3,5-dihydroimidazol-4-one **7** for Knoevenagel reaction, we have also examined the reactivity of **7** with cycloketones **10a–d**



Scheme 2 Knoevenagel reactions obtained from 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one **7** with aromatic aldehydes **8**, cycloketones **10** and ketones **12**.

Table 1 Results of Knoevenagel reactions of **7** with aromatic aldehydes **8a–f** in refluxing methylene chloride (method A) and at 70 °C under focused microwave irradiations using solvent-free conditions (method B)

Aldehyde		Product **9**	Yield of **9**[a] (%)		Reaction time		mp of **9**[f]/°C
			Method A[b]	Method B[c]	Method A[d]	Method B[e]	
	**8a**	**9a**	71	82	1.5 h	15 min	102–104
	**8b**	**9b**	76	84	4 h	15 min	122–124
	**8c**	**9c**	82	78	4 h	15 min	124–126
	**8d**	**9d**	90	95	2 h	25 min	181–183
	**8e**	**9e**	85	94	8 h	20 min[g]	155–157
	**8f**	**9f**	87	92	8 h	20 min	195–197

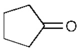
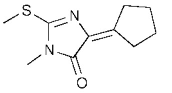
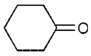
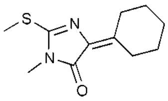
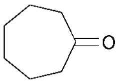
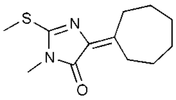
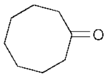
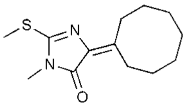
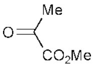
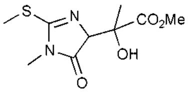
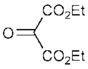
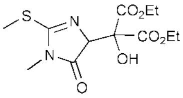
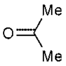
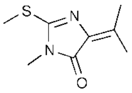
[a] Yield of isolated product. [b] Reactions were run in a thermostatted oil bath, variation ±1 °C. [c] Microwave irradiation by focused oven (Synthewave® 402, Prolabo). [d] The reaction time was determined by TLC with precoated plates of silica gel 60F 254 (Merck). [e] The reaction time was determined by ^{1}H NMR spectroscopy from the crude reaction mixture ($CDCl_3$, Bruker AC 300P, TMS as internal reference). [f] Melting points were determined on a Kofler melting point apparatus and are uncorrected. [g] The reaction temperature was 90 °C.

and acetone **12c** using the reaction conditions of method B (Scheme 2). The results obtained and the isolated yields of products **11a–d** and **14c** are given in Table 2. The compounds **11a–c)** and **14c** were produced in good yields (73–94%) and required a short reaction time (15–45 min) except for **11d** derived from cyclooctanone (10% yield after a reaction time of 90 min).

During the course of our work, we have also found that reaction of **7** with methyl pyruvate **12a** and diethyl ketomalonate **12b** according to the method B afforded quantitatively the respective hydroxy imidazolone **13a** and **13b** after 15 min (Scheme 2). Initial attempts to force the reaction to completion, with one equivalent of piperidine and long reaction time, were unsuccessful (no amount of imidazolone **14** was detected in the ^{1}H NMR spectrum of the crude reaction mixture).

In summary, we have developped a versatile and useful new access to 5-ylidene-3,5-dihydroimidazol-4-ones and precursor of Leucettamine B using the eco-friendly solventless method-

Table 2 Results of condensation reactions of 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one **7** with cyloketones **10a–d** and ketones **12a–c** using solvent-free conditions under focused microwave irradiations (method B

Ketone[a]		Product		Reaction time[b]	Temperature/°C	Yield[c] (%)
10a		**11a**		15 min	70	84
10b		**11b**		30 min	90	94
10c		**11c**		45 min	128	73
10d		**11d**		1.5 h	135	10
12a		**13a**		15 min	70	90
12b		**13b**		15 min	70	93
12c[d]		**14c**		15 min	56	92

[a] 1 equiv. of **12** was used. [b] The reaction time was determined by ^{1}H NMR spectroscopy from the crude reaction mixture ($CDCl_3$, Bruker AC 300P, TMS as internal reference). [c] Yield of isolated product. [d] **12c** was used as solvent.

ology assisted by focused microwave heating. Work is now in progress to study the pharmaceutical potentialities of these new imidazolones.

Experimental

General procedure using a focused microwave oven for condensation reactions of aromatic aldehydes 8a–f with 7

In a cylindrical quartz tube (diameter = 4 cm) were placed successively 3-methyl-2-methylsulfanyl-3,5-dihydro-imidazole-4-one **7** (1 g, 6.9 mmol), a freshly distilled aromatic aldehyde **8** (6.9 mmol.) and 5% of piperidine (0.029 g, 0.34 mmol). Then, this tube was introduced into a Synthewave® 402 Prolabo microwave reactor [2.45 GHz, adjusted power within the range 0–300 W and a wave guide (single mode T01) fitted with a stirring device and an IR temperature detector]. Microwave irradiation was carried out at 70 °C during the appropriate reaction time. The mixture was allowed to cool down. After addition of methylene chloride (*ca*. 20 mL), the organic layer was treated three times with water (3 × 7 mL), dried over anhydrous $MgSO_4$ and filtered. Removal of solvent *in vacuo* lead to a viscous oil that crystallized rapidly. The crude residue was purified by recrystallization from pentane (or eventually by chromatography on silica gel 60F 254 (Merck) with appropriate eluent) and the desired compound **9** was characterized by ^{1}H, ^{13}C NMR and HRMS analysis.

Selected spectral data

3-Methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one 7. HRMS, *m/z* : M+ 144.0360 (calc. for C5H9N2OS : 144.0357); mp 80–82 °C (from pentane). ^{1}H NMR (300 MHz, CDCl3, TMS as internal ref.) δ 2.56 (s, 3H), 3.06 (s, 2H), 4.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.35 (q, *J* 143 Hz), 26.24 (q, *J* 141 Hz), 58.97 (t, *J* 144 Hz), 164.23 (sm, C-4), 180.00 (sm, C-2).

(5*Z*)-5-Benzylidene-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one 9a. HRMS, *m/z* : M+ 232.0669 (calc. for $C_{12}H_{12}N_2OS$: 232.0670); mp 102–104 °C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 2.71 (s, 3H), 3.13 (s, 3H), 6.93 (s, 1H, =CH), 7.28–7.40 (m, 2H, Ar), 8.14 (d, 2H, *J* 7.4 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.90 (q, *J* 144 Hz), 26.47 (q, *J* 140 Hz), 123.71 (dt, *J* 156, 4.8 Hz, =CH), 128.58 (dd, *J* 160, 7.5 Hz), 129.67 (dt, *J* 161, 7.6 Hz), 131.87 (dm, *J* 162 Hz), 134.45 (t, *J* 7.4 Hz, C-1′), 138.45 (s, C-5), 165.38 (sm, C-4), 169.97 (sm, C-2).

(5*Z*)-5-(4-Bromobenzylidene)-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one 9c. HRMS, *m/z*: M^+ 309.9775 (calc. for $C_{12}H_{11}N_2{}^{79}BrS$: 309.9775); mp 155–157 °C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 2.71 (s, 3H), 3.14 (s, 3H), 6.83 (s, 1H, =CH), 7.75 (dd, *J* 8.5 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.95 (q, *J* 144 Hz), 26.50 (q, *J* 141 Hz), 122.04 (dt, *J* 157, 4.7 Hz, =CH), 124.01 (sm, C-4′), 131.39 (dd, *J* 166, 5.7 Hz, C-3′, C-5′), 133.13 (dt, *J* 164, 6.4 Hz, C-2′, C-6′), 133.38 (t, *J* 7.7 Hz, C*ipso*), 138.84 (s, C-5), 166.01 (sm, C-4), 169.75 (sm, C-2).

(5*Z*)-5-Benzo[1,3]dioxol-5-ylmethylene-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one 9f. HRMS, *m/z*: 276.0576 (calc. for $C_{13}H_{12}N_2O_3S$: 276.0569); mp = 195–197 °C (from pentane) (Lit.[6] : 195.2 °C). ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 2.71 (s, 3H), 3.14 (s, 3H), 6.00 (s, 2H), 6.82 (d, 1H, *J* 8.1 Hz), 6.86 (s, 1H, =CH), 7.37 (dd, 1H, *J* 8.1, 1.5 Hz), 8.04 (d, 1H, *J* 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.92 (q, *J* 144 Hz), 26.48 (q, *J* 141 Hz), 101.41 (t, *J* 174 Hz), 108.44 (d, *J* 165 Hz, C-2′), 110.87 (dt, *J* 167, 7.2 Hz, C-6′), 123.83 (ddd, *J* 156, 5.5, 4.3 Hz, =CH), 128.05 (dt, *J* 162, 6.2 Hz, C-5′), 129.07 (sm, C-3′), 137.05 (s, C-5), 147.95 (sm, C-1′), 149.09 (sm, C-4′), 164.17 (sm, C-4), 169.95 (sm, C-2).

Diethyl 2-hydroxy-2-(1-methyl-2-methylsulfanyl-5-oxo-4,5-dihydro-1*H*-imidazol-4-yl)malonate 13b. HRMS, *m/z*: 318.0884 (calc. for $C_{12}H_{19}N_2O_6S$: 318.0886); mp 94–96 °C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 1.34 (m, 6H), 2.55 (s, 3H), 3.01 (s, 3H), 3.95 (br. s, 1H, OH), 4.35 (m, 4H), 5.00 (s, 1H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.84 (q, *J* 143 Hz), 14.39 (q, *J* 127 Hz), 26.73 (q, *J* 140 Hz), 63.56 (t, *J* 146 Hz), 63.67 (t, *J* 146 Hz), 72.04 (d, *J* 149 Hz), 79.44 (d, *J* 5.8 Hz), 166.27 (sm, C-4), 168.32 (sm, CO), 167.98 (sm, CO), 177.98 (sm, C-2).

5-methylethylidene-3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one 14c. HRMS, *m/z*: 184.0671 (calc. for $C_8H_{12}N_2OS$: 184.0670); mp 65–67 °C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 2.17 (s, 3H), 2.19 (s, 3H), 2.68 (s, 3H), 3.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) δ 12.37 (q, *J* 143 Hz), 19.01 (qq, *J* 128, 4.6 Hz, Me_2C=), 21.94 (qq, *J* 128, 4.4 Hz, Me_2C=), 26.17 (q, *J* 140 Hz), 133.66 (C-5), 144.71 (=CMe_2), 158.54 (sm, C-4), 167.89 (sm, C-2).

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15 Isobutyl glycinate **3** is stable at room temperature (*ca*. 18 h) but it is recommended that it should be handled under an inert atmosphere at 4 °C (no decomposition observed after 2 days). *1*H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) δ 0.93 (d, 6H, *J* 6.7 Hz), 1.58 (br s, 2H), 1.94 (tm, 1H, *J* 6.7 Hz), 3.44 (s, 2H), 3.92 (d, 2H, *J* 6.7 Hz).

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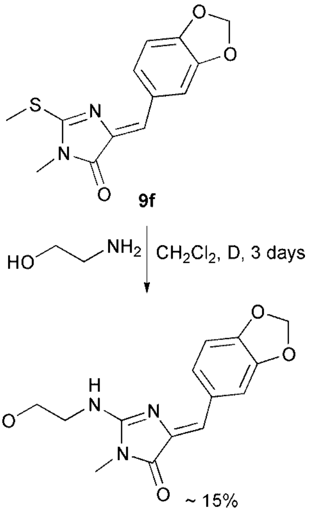
18 The displacement of the MeS group of **9f** with ethanolamine in methylene chloride gave the 2-hydroxyethylamino derivative of *Leucettamine B* in poor yield (*ca*. 15%) after a reaction time of 3 days.



Initial attempts to obtain the *N*-alkyl derivatives of *Leucettamine B* from **9f** with various alkylamines using solvent-less conditions were unsuccessful.

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Reaction of butane to isobutane on silica-supported 12-tungstosilicic acid

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The heteropolyacids 12-tungstosilicic acid (TSA), 12-tungstophosphoric acid (TPA), 12-molybdosilicic acid (MSA) and 12-molybdophosphoric acid (MPA) were supported on SiO_2 and examined in the gas–solid phase reaction of butane to isobutane. Use of a support was effective for TSA and TPA whereas no reaction was observed with MSA or MPA. Effectiveness of the support for TSA was observed with ZrO_2 and Al_2O_3 but not with TiO_2, SnO_2, or Fe_2O_3. The most active catalyst was prepared by impregnating SiO_2 with an aqueous solution of 40 wt% TSA followed by water evaporation and heat-treating in air at 300 °C (40% TSA/SiO_2). The catalytic activity was more than doubled when a physical mixture of 40% TSA/SiO_2 and Pt/ZrO_2 was used.

Introduction

The increasing demand for branched hydrocarbons to meet stringent gasoline components has led to an important search for efficient catalysts. These gasoline components are produced from acid-catalyzed reactions such as isomerization and alkylation. The catalysts used in the commercial processes that produce branched hydrocarbons still suffer from several disadvantages particularly related to environmental problems. For instance, in the alkylation of isobutane with butenes to obtain high octane gasoline, concentrated H_2SO_4 or HF are used as catalysts, presenting not only an environmental threat but also difficulty in their separation from the products. On the other hand, a commercial catalyst for the isomerization of lower *n*-alkanes is Pt- and Cl-containing Al_2O_3 which is sensitive to water and requires constant addition of alkyl chlorides to recover acid functionalities. Environmental concerns about the use of toxic Friedel–Crafts catalysts ($AlCl_3$, BF_3, *etc.*) and liquid inorganic acids in the transformation of hydrocarbons provide an impetus for a search of stable and more environmentally friendly solid acid catalysts. The skeletal rearrangement of butane into isobutane, catalyzed by strong acid catalysts, is of great interest since isobutane is a key component for the manufacture of valuable gasoline additives such as trimethylpentanes and methyl *tert*-butyl ether.

Heteropolyacids are efficient catalysts for various reactions in the liquid phase, *e.g.* hydration, esterification and isomerization. They usually show catalytic activities higher than ordinary solid acids such as zeolites and silica-alumina. Owing to their small surface areas (1–10 $m^2\ g^{-1}$) heteropoly compounds are supported on SiO_2, SiO_2-Al_2O_3, TiO_2 or activated carbon when used as catalysts for gas–solid phase reactions,[1–4] alcohol dehydration,[5,6] carboxylic acid decomposition,[7] butene structural isomerization,[8] and methanol conversion.[9] To our knowledge, there have been no reports on SiO_2-supported heteropolyacids which are active for the skeletal isomerization of the less reactive butane. Attempting to develop strong solid acid catalysts, we selected 12-tungstosilicic and 12-tungstophosphoric acids, which show high acidities among Keggin-type heteropolyacids, and impregnated them on SiO_2. In this study we report on the preparation of $H_4[SiW_{12}O_{40}]/SiO_2$ and $H_3[PW_{12}O_{40}]/SiO_2$ and their catalytic activities for the gas–solid phase isomerization of butane to isobutane.

Experimental

The silica-supported heteropolyacids (HPAs), HPA/SiO_2, were prepared by impregnating SiO_2 (Shinwa Chemical Industries, Ltd., S-20D) with an aqueous solution of 12-tungstosilicic acid (TSA), $H_4[SiW_{12}O_{40}]$, 12-tungstophosphoric acid (TPA), $H_3[PW_{12}O_{40}]$, 12-molybdosilicic acid (MSA), $H_4[SiMo_{12}O_{40}]$, or 12-molybdophosphoric acid (MPA), $H_3[PMo_{12}O_{40}]$, followed by evaporation of water, drying, and heating in air at 300 °C for 3 h. The wt% of HPA is defined as HPA/(SiO_2 + HPA). TSA catalysts supported on other metal oxides were prepared in the same manner as TSA/SiO_2. The metal hydroxides were obtained by hydrolysing $ZrOCl_2$, $TiCl_4$, $SnCl_4$ or $FeCl_3$ with aqueous ammonia. γ-Al_2O_3, supplied from the Catalysis Society of Japan as a reference catalyst denoted ALO-1, was also used. Pt/ZrO_2 was obtained by impregnating zirconia gel with aqueous hydrogen hexachloroplatinate(IV) hexahydrate ($H_2PtCl_6\cdot 6H_2O$); this was followed by evaporation of water, drying, and calcining in air at 750 °C for 3 h, the concentration being 0.5 wt% Pt based on the gel.

Reactions for butane were carried out in a microcatalytic pulse reactor with a fixed-bed catalyst connected to an on-line gas chromatograph [He carrier gas 20 ml min^{-1}; pulse size 0.05 ml (gas): VZ-7, 6 m, 0–30 °C for GC analysis]. Gaseous reactants were introduced *via* a syringe and passed through the catalyst bed. The catalyst was again heated at 300 °C for 1 h in the He flow before reaction; the quantity of catalyst used was equivalent to that of 0.1 g of HPA, *i.e.* 0.1, 0.25 and 0.3 g for

Green Context

The isomerisation of *n*-butane to isobutane is an important process for the development of advanced fuels. This is carried out by the use of a Pt/Cl-alumina catalyst which has many drawbacks in terms of stability and lifetime. This paper deals with the use of heteropolyacids supported on silica as acid catalysts for its valuable transformation. Conversions are relatively good, and are enhanced significantly by the addition of a small amount of Pt-zirconia to the catalyst. ***DJM***

Table 1 Activities of catalysts for the reaction of butane

Catalyst (amount)	T/°C	Conversion (%)	Products C_3H_8	 i-C_4H_{10}	 C_5H_{12}
TSA (0.1 g)	220	0.3		0.3	
TPA (0.1 g)	220	3.4	0.4	2.8	0.2
MSA (0.1 g)	220	Trace			
MPA (0.1 g)	220	Trace			
33% TSA/SiO_2 (0.3 g)	220	12.3	1.5	10.1	0.7
40% TSA/SiO_2 (0.25 g)	220	15.2	2.4	12.0	0.8
40% TSA/SiO_2 (0.25 g)	240	21.9	5.8	14.8	1.3
40% TSA/SiO_2 (0.25 g)	260	27.4	9.9	15.9	1.6
33% TPA/SiO_2 (0.3 g)	220	5.8	0.6	4.9	0.3
40% TPA/SiO_2 (0.25 g)	220	8.6	0.8	7.4	0.4
40% TPA/SiO_2 (0.25 g)	260	13.2	2.8	9.6	0.8
33% MSA/SiO_2 (0.3 g)	220	0			
33% MPA/SiO_2 (0.3 g)	220	0			
33% TSA/ZrO_2 (0.3 g)	220	6.7	1.2	4.9	0.6
33% TSA/Al_2O_3 (0.3 g)	220	4.2	0.3	3.8	0.1
33% TSA/TiO_2 (0.3 g)	220	0			
33% TSA/SnO_2 (0.3 g)	220	0			
33% TSA/Fe_2O_3 (0.3 g)	220	0			
0.5% Pt/Al_2O_3[a]	220	0.6[b]			
40% TSA/SiO_2 (0.25 g) + Pt/ZrO_2) (0.2 g)[c]	220	36.0	12.0	22.0	2.0
40% TPA/SiO_2 (0.25 g) + Pt/ZrO_2 (0.2 g)[c]	220	31.6	9.8	19.9	1.9

[a] A reference catalyst supplied from the Catalysis Society of Japan, JRC-A4-0.5Pt heat-treated in air at 500 °C. [b] Products: CH_4, C_2H_6, C_3H_8 and C_4H_8. [c] A physical mixture.

solid TSA, 40% TSA/SiO_2 and 33% TSA/SiO_2, respectively. Activities were taken as the average of the 6–10th pulse values.

Results and discussion

The reaction of butane was carried out at 220 °C and 20 ml min^{-1} of He carrier over 0.1 g of solid TSA, TPA, MSA or MPA (dried at 300 °C). Low conversions were observed for short contact times under the conditions used as shown in Table 1. The conversion was, however, promoted when TSA was supported on SiO_2; supporting was also effective for TPA but not for MSA or MPA. The wt% of supported reagent had an effect on the conversion, with the 40 wt% support being more effective than the 33 wt% support for both TSA and TPA; 40% TSA/SiO_2 gave 27.4% conversion for reaction at 260 °C. The chief product was isobutane formed from butane by skeletal isomerization; propane was also observed in addition to small amounts of pentane. The selectivity for isobutane was higher at lower temperatures: 79, 68 and 58% at 220, 240 and 260 °C, respectively, for 40% TSA/SiO_2.

The effect of supporting for TSA was also observed with ZrO_2 and Al_2O_3, though SiO_2 was most effective; no reaction however, was observed for TiO_2, SnO_2, and Fe_2O_3 (Table 1). An affinity of TSA towards the silica substance seems to be related with the supporting effect. A commercial Pt-based alumina catalyst was tested, but no isomerization was observed.

The effect of modifying the proportion of TSA in the catalyst was studied. The maximum activity was observed at 40 wt% for SiO_2 and with 20% for ZrO_2. For ZrO_2 catalysts with 10 and 33% TSA slightly lower activities were observed as shown in Fig. 1. The 40 wt% level was also efficient for TPA when supported on SiO_2.

The heat resistance of TSA was examined with the conversions of butane over the supported catalysts heat-treated at various temperatures (along with that of unsupported solid TSA without support for reference) shown in Fig. 2. Steady activity was observed for treatment at 275–325, 300–375 and 300 °C for the SiO_2, ZrO_2 and Al_2O_3 materials, respectively. Given the inactivity of solid TSA heated at 350 °C, it is proposed that a preparation temperature of 300 °C is most satisfactory.

In previous papers,[10–12] we reported the catalysis of solid superacids, sulfated metal oxides and zeolites upon mechanically mixing with platinum-supported zirconia (Pt/ZrO_2) for the reaction of butane to isobutane. The activities of the catalysts were largely promoted by addition of Pt/ZrO_2, and were much

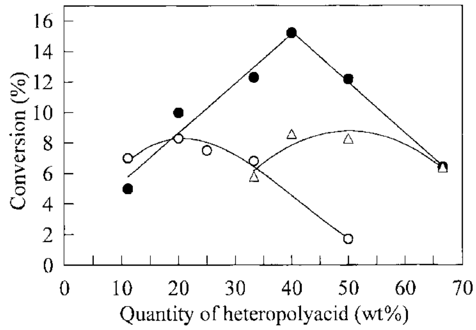

Fig. 1 Activities of TSA/SiO_2 (●), TSA/ZrO_2 (○) and TPA/SiO_2 (△) catalysts with various wt% of heteropoly acids for the conversion of butane at 220 °C.

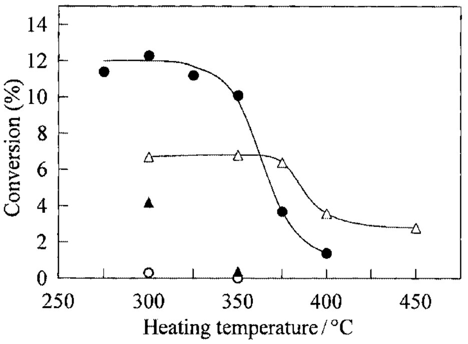

Fig. 2 Activities of catalysts heated at various temperatures for the conversion of butane at 220 °C. 33% TSA/SiO_2 (0.3 g)(●), 33% TSA/ZrO_2 (0.3 g) (△), 33% TSA/Al_2O_3 (0.3 g) (▲), TSA alone (0.1 g) (○).

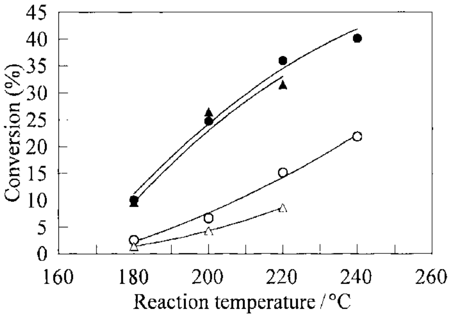

Fig. 3 Activities of catalysts for the reaction of butane: 40% TSA/SiO_2 (0.25 g) (○), 40% TPA/SiO_2 (△), 40% TSA/SiO_2 (0.25 g) + Pt/ZrO_2 (0.2 g) (●), 40% TPA/SiO_2 (0.25 g) + Pt/ZrO_2 (0.2 g) (▲).

higher than those of the Pt-supported superacids prepared by the addition of Pt to superacids. Following this method, 0.2 g of Pt/ZrO_2 and 0.25 g of 40% TSA/SiO_2 or 40% TPA/SiO_2 were mixed well using a mortar and pestle and examined in the reaction of butane; the effect of mixing was remarkable (Table 1) with 36.0 and 31.6% conversion at 220 °C with 61 and 63% selectivity for isobutane for TSA and TPA, respectively. This mixing effect was examined in the temperature range 180–240 °C, results being shown in Fig. 3 along with those without mixing for comparison. The activity was more than doubled at each temperature for both TSA and TPA. The coversion also increased essentially linearly with temperature.

In summary, this work has addressed an important opportunity related to green chemistry where a silica-supported 12-tungstosilisic acid catalyst leads to a new gas-solid phase reaction which is an environmentally benign process in the reaction of butane to isobutane. The catalytic effect was promoted by mixing Pt/ZrO_2 physically with the catalyst.

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Uncatalysed reactions in water: Part 2.† Preparation of 3-carboxycoumarins

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A simple, efficient and environmentally friendly procedure has been developed for the reaction of Meldrum's acid with salicylaldehydes. 3-Carboxycoumarins **5** were synthesised in high yields (78–96%) and excellent selectivities (95–98%) by carrying out the reaction in water at reflux for 10 h, avoiding the addition of any catalyst.

Introduction

Owing to stringent and growing environmental regulations, the modern chemical industry is prompted to minimize as much as possible waste production and hazardous substance use in chemical manufacture.[2] To this end polluting technologies must be replaced by benign alternatives; moreover, as clearly stressed by Collins, '*this field is receiving considerable attention, but the dedicated research community is small and is merely scratching the surface of an immense problem*'.[3]

Since the revision of fundamental synthetic reactions for fine chemicals production under environmentally friendly conditions represents the main subject of our research group,[4] we have recently examined the synthesis of 3-carboxycoumarins. Coumarin (2*H*-1-benzopyran-2-one) and coumarin derivatives are natural compounds[5] and are important chemicals in perfume, cosmetic and pharmaceutical industrial production.[6] These compounds are usually prepared *via* condensation of salicylic aldehydes with malonic acid or esters (Knoevenagel reaction) under base catalysis.[7]

In recent years much effort has been devoted to preparing coumarin derivatives following greener approaches by using sodium hydroxide in water,[8] zeolites,[9] clays,[10] cation-exchanged resins[11] or solventless conditions.[12] A solid phase approach has also been utilised.[13]

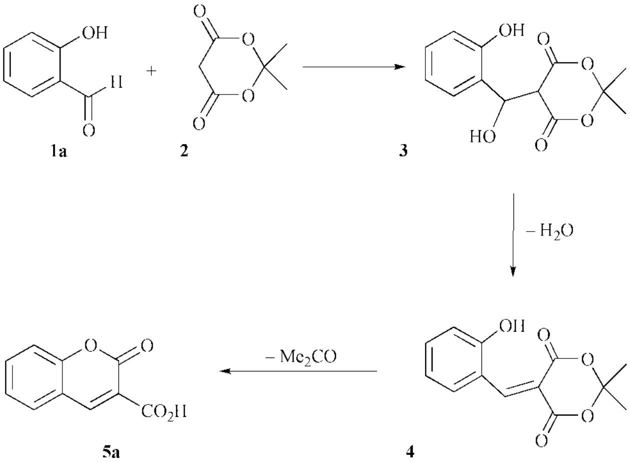
Results and discussion

By paraphrasing the concept reported by Sheldon *'the best solvent is no solvent'*,[14] we can state that *the best catalyst is no catalyst*; on this subject, in a recent paper some of us reported the uncatalysed preparation of ylidenemalononitriles in water. The reaction, carried out by reacting malononitrile with aromatic, heteroaromatic or aliphatic aldehydes in water, afforded the corresponding condensation products in high yields and selectivities.[1]

As an extension of this work, we decided to try to synthesise the 3-carboxycoumarins **5** by reacting salicylic aldehydes **1** with a suitable C–H acid containing compound such as Meldrum's acid **2** without addition of any catalyst (Scheme 1).

This readily available compound 2,2-dimethyl-1,3-dioxan-4,6-dione (**2**) has been utilised synthetically as source of acetyl units for the synthesis of β-keto esters,[15] β-keto anilides,[16] malonodiamides[17] and for the three component preparation of β-substituted tryptophans[18] or pyrrolidinones.[19] More recently it has been utilised in the ammonium acetate catalysed synthesis of substituted coumarins.[12]

We first estimated the reactivity of the model reaction between salicylic aldehyde **1a** (10 mmol) and Meldrum's acid **2** (12 mmol) in water at reflux: after 10 h the corresponding 3-carboxycoumarin **5a** was isolated in 93% yield and in 98% selectivity. The separation and purification processes are very simple, as they involve only a Buchner funnel filtration and washing with water (10 ml).



Scheme 1

Green Context

The simplification of reaction protocols is an important concept in designing new clean methodologies. Avoiding unnecessary reagents, protecting groups *etc.* is a key element in the construction of improved methodologies. This paper contributes to this theme in an unusual way removing the catalyst. The authors have shown that very efficient reactions can be achieved in the condensation of Meldrum's acid with salicylaldehydes, leading to carboxycoumarins using water as solvent. The process is thus much simpler than conventional routes, and has a very simple isolation procedure. ***DJM***

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† Part 1: ref. 1.

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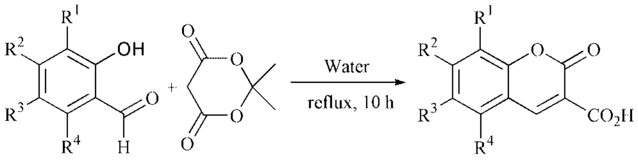
Attempts to perform the reaction under solventless conditions resulted in a modest yield decrease (78%) while maintaining good selectivity (96%).

It is interesting that the reaction easily occurs in water although the mechanism involves a net dehydration of the alcoholic intermediate **3** obtained by nucleophilic attack of the active methylene of **2** to the carbonyl group of **1**; the ease of the dehydration process is ascribable to the extent of C=C double bond conjugation in **4**. Similar unexpected solvent effects have also been previously found by other authors[20] and by ourselves.[10,21]

In a second series of experiments we explored the general validity of the present methodology; different 3-carboxycoumarins **5** were synthesised in 78–96% yield and 95–98% selectivity (Table 1, entries a–f).

It must be underlined that salicylic aldehydes bearing lipophilic substituents (Table 1, entries g and h) were recovered unchanged after the reaction; this is probably due to the practically complete insolubility of these starting materials in water. In addition, the slightly lower yields obtained in the reactions with salicylic aldehydes **1e–f** seem to confirm this hypothesis. In all cases the intermediates **3** and **4** were never isolated.

Table 1 Uncatalysed synthesis of 3-carboxycoumarins



1 **2** **4**

Entry	R¹	R²	R³	R⁴	**5** Yield [select.[a]] (%)
a	H	H	H	H	93 [98]
b	OMe	H	H	H	95 [98]
c	OH	H	H	H	96 [97]
d	Me	OH	H	H	83 [95]
e	Cl	H	Cl	H	78 [98]
f	H	H	CH–CH=CH–CH		80 [96]
g	Buᵗ	H	Me	H	—
h	Buᵗ	H	Buᵗ	H	—

[a] (Yield of 5/conversion of 1) × 100.

Conclusions

In conclusion, we have found that coumarin-3-carboxylic acids can be synthesized in high yields and selectivities from substituted salicylic aldehydes and Meldrum's acid with no added catalyst; the use of water as reaction solvent, as reported by Breslow,[22] gives environmental benefits, *i.e.* no atmospheric pollution by escaping solvents, easy waste treatment (water is easy to purify); in addition the product separation involves only a simple filtration. For these reasons this methodology represents an important improvement for the production of this kind of fine chemicals following environmentally benign procedures.

Experimental

Typical procedure

In a round-bottomed flask the selected salicylaldehyde (10 mmol) and Meldrum's acid (12 mmol) in water (20 ml) were heated at reflux under stirring for 10 h; then, the reaction mixture was cooled and filtered on Büchner funnel. The products were purified, if necessary, by crystallization from ethyl acetate or methanol.

All the known products gave melting points and spectral data consistent with reported values.

Acknowledgements

We acknowledge the support of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy, and the University of Parma (National Project 'Processi Puliti per la Chimica Fine'). We are also grateful to the Centro Interfacoltà Misure (C.I.M.) for the use of NMR and mass spectrometry instruments.

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Green approach to substituted carbohydrates: telomerisation of butadiene with sucrose

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The etherification of sucrose in aqueous solutions is performed *via* butadiene telomerization catalysed by palladium complexes. The degree of substitution is evaluated from a combination of analytical techniques including NMR and LSIMS as well as chromatographic and gravimetric measurements. Degrees of substitution ranging from 1 to 6 are obtained depending upon the experimental conditions, particularly temperature, butadiene/sucrose ratio and the nature of catalyst. Thus, the palladium precursor salt and the use of optimum amounts of TPPTS ligand are shown to be critical parameters. The solubility in water of the modified sucrose molecules are substantially modified.

Introduction

The application of sucrose derivatives as surfactants, plastics or polymers is attractive because this pure and cheap carbohydrate is a renewable polyfunctional starting material. Moreover, many new sugar based products present the advantage of being non-toxic and biodegradable.[1] Many routes are available for the synthesis of mono- or poly-ethers, among them the Williamson synthesis which is one of the most widely used.[2] However, this approach leads to the formation of stoichiometric amounts of salts, which is undesirable. An alternative route for the preparation of long-chain substituted ethers is based on the telomerisation of butadiene with alcohols, usually using palladium complexes as catalysts.[3] This reaction has been largely studied with different nucleophiles such as alcohols, phenol, carboxylic acids, amines and compounds with active methylene groups. Using carbohydrates as nucleophiles the reaction leads to hydrophobic alkyl saccharides which may show interesting physical and chemical properties.

As far as sucrose is concerned, it was shown that using Pd/TPPTS as catalyst with $\mathrm{Pr^iOH}$–1 M NaOH (aq) as solvent, a mixture of mono- and di-substituted sucrose was mainly obtained.[4] For the telomerization of butadiene with alcohols, it was demonstrated that the nature of the catalytic complex, the molar ratio butadiene/alcohol, the temperature, and the reaction time have a remarkable influence on the conversion and the selectivity of theses reactions.[5] Our objective was to establish the influence of the various reaction parameters on the degree of substitution rather than to prepare a single product. To achieve this goal substantial effort was made to develop a set of analytical methods to determine the degree of substitution, which is commonly used to establish the transformation rate of such reactions,[4] as well as the nature of the products.

Results and discussion

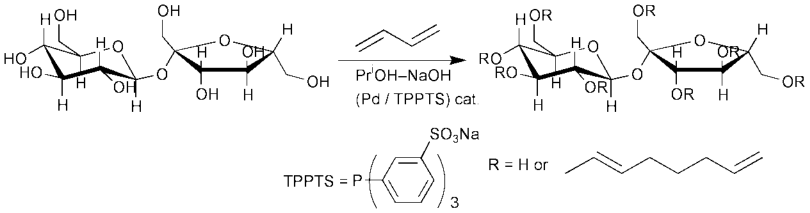
Preliminary experiments

When the reaction was performed in water, no transformation occurred probably because butadiene is not soluble in water. In $\mathrm{H_2O}$–$\mathrm{Pr^iOH}$ mixture, reaction occurred but LSIMS analysis showed that some hydroxyl groups were substituted with $\mathrm{C_4}$ groups (degenerated telomerisation). In contrast in an 1 M NaOH (aq)–$\mathrm{Pr^iOH}$ mostly $\mathrm{C_8}$ alkyl chains were detected as shown in Fig. 1 in which peaks at m/z = 581, 689, 797, 905, corresponding to the mono, di , tri and tetra-ethers were observed, however, smaller peaks at m/z 635, 743 were also

Green Context

The use of non-fossil based renewable feedstocks for the manufacture of chemicals will become increasingly important in the 21st century. Sucrose is the cheapest carbohydrate and offers a high density of functional groups making it a very attractive starting material for the preparation of new and useful materials. Etherification is a common functionalisation method for such a hydroxyl-rich material but traditional methods of etherification are wasteful and rather negate the use of 'greener' starting materials. Here a much cleaner etherification method based on butadiene telomerization with a very active metal catalyst is described. A range of degrees of substitution can be achieved in this atom-efficient and low-waste process.

JHC



Scheme 1 Synthesis of polysubstituted sucrose.

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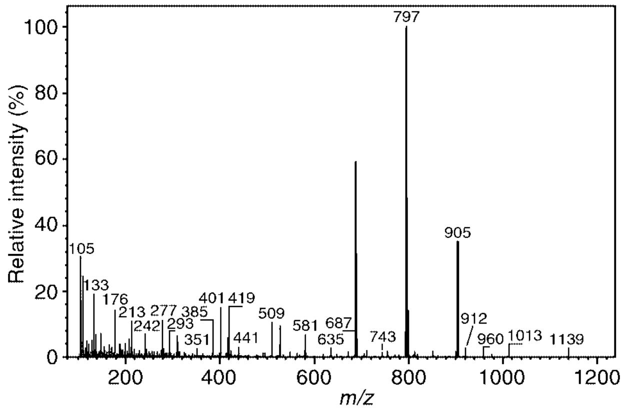

Fig. 1 Typical LSIMS analysis. *Reaction conditions*: 4 g sucrose, 20 mg Pd(OAc)$_2$, 150 mg TPPTS, 5 ml 1 M NaOH (aq), 17.5 ml Pr^{i}OH, 80 °C; butadiene/sucrose = 30.

detected indicating that C_4 adducts were always present. Subsequent reactions were conducted under the latter conditions.

The evolution of the degree of substitution (DS) *vs*. time determined by weight measurement or NMR analysis is shown in Fig. 2. Both curves have similar shape and show a fairly good match.

GC analysis indicated that after 30 min reaction, sucrose was fully recovered while conversion was complete after 24 h. As expected, the longer the reaction time, the higher the degree of substitution. After 24 h, a high substitution level was observed by NMR analysis while the weight increased by 170% which corresponds to a degree of substitution of *ca*. 6. Both GC and LSIMS measurements indicated that for long reaction times neither sucrose nor its monoether were present in the medium.

The temperature was a critical parameter, no transformation occurred at 40 °C even after 12 h reaction. It was necessary to conduct the reaction at least at 60 °C to observe some conversion (DS = 2 to 3) while at 80 °C, NMR analysis of the acetylated product indicated that almost all the hydroxyl groups were substituted.

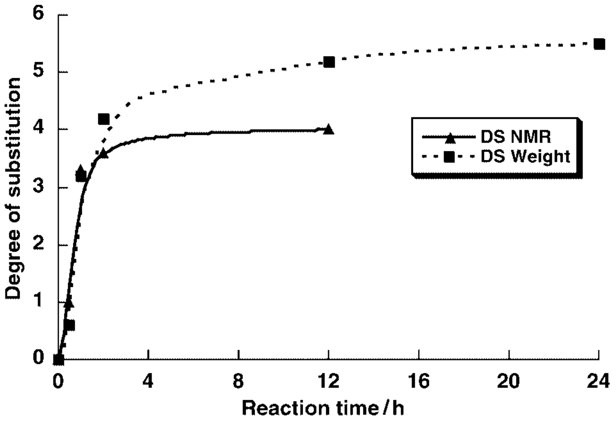

Fig. 2 Degree of substitution *vs*. time for telomerisation of sucrose. *Reaction conditions*: 4 g sucrose, 10 mg Pd(OAc)$_2$, 75 mg TPPTS, 5 ml 1 M NaOH (aq), 17.5 ml Pr^{i}OH, 80 °C, butadiene/sucrose = 20.

Influence of butadiene concentration

As the butadiene/sucrose molar ratio was increased from 10 to 38, the DS calculated from weight uptake or from NMR integrations increased as shown in Table 1.

Using butadiene in sub-stoichiometry (< 16), a very low degree of substitution was observed (< 1). Under stoichiometric conditions, the weight increased up to 90% which corresponds to about two ether groups per sucrose molecule. With a large excess of butadiene (B/S = 38) a weight uptake of 106% was achieved, *i.e*., half of the hydroxyl groups were substituted.

Table 1 Influence of the butadiene/sucrose ratio on the DS of sucrose[a]

Butadiene/ sucrose (mol/mol)	Weight uptake (%)	DS$_{\text{Weight}}$[b]	DS$_{\text{NMR}}$[c]
10	0	0	0
14	16	0.5	0.8
16	90	2.8	1.8
38	106	3.4	3

[a] *Reaction conditions*: 4 g sucrose, 10 mg Pd(OAc)$_2$, 75 mg TPPTS, 5 mL 1 M NaOH (aq), 17.5 ml Pr^{i}OH, 2 h, 80 °C. [b] Calculated from weight uptake. [c] Calculated from ^{1}H NMR analysis.

Influence of ligand/metal ratio

The influence of ligand/metal ratio was studied to optimise the amount of expensive TPPTS ligand used.

The data given in Fig. 3 show that the highest degree of substitution was observed for TPPTS/metal = 3. However, when using 1.4 equivalents of TPPTS, approximately half of the hydroxyl groups were substituted. When the ligand was used in a large excess (5 equivalents) it acted as a poison and the degree of substitution was lowered.

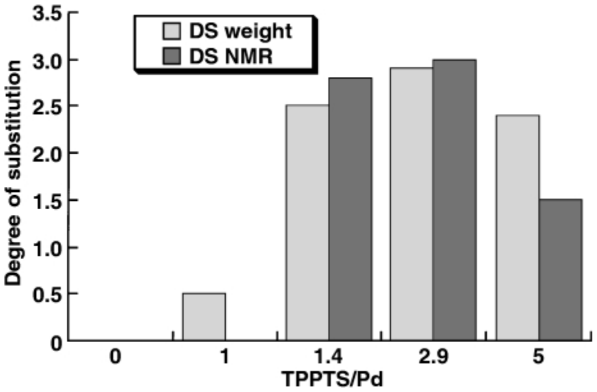

Fig. 3 Influence of the TPPTS/Pd ratio on the degree of substitution. *Reaction conditions*: 4 g sucrose, 20 mg Pd(OAc)$_2$, 5 ml 1 M NaOH (aq), 17.5 ml Pr^{i}OH, 80 °C; butadiene/sucrose = 20–25.

Influence of metal precursors

Several metallic precursors associated with TPPTS were tested and the results are reported in Table 2.

Nickel and cobalt based catalysts were not very efficient for this reaction. For the palladium based catalysts, a similar

Table 2 Influence of the nature of catalyst on the DS of sucrose[a]

Precatalyst	Weight uptake (%)	DS$_{\text{NMR}}$	Conversion[b] (%)
Ni(OAc)$_2$	21	0	n.d.
Co(OAc)$_2$	24	0.4	n.d.
Pd(OAc)$_2$	90	3.1	90
PdCl$_2$	92	2.5	90
Pd(NO$_3$)$_2$	87	2.8	> 95
Pd(NH$_3$)$_4$Cl$_2$	44	1.2	60

[a] *Reaction conditions*: 4 g sucrose, butadiene/sucrose = 20–25, 5 ml 1 M NaOH (aq.), 17.5 ml Pr^{i}OH, 2 h, 80 °C. [b] Determined by GC.

conversion was achieved whatever the precursor salt except for the tetrammine palladium complex which gave a lower conversion. The $Pd(OAc)_2$ catalyst precursor was the most efficient for this type of reaction and a high degree of substitution was obtained.

In conclusion, we have demonstrated a quick and convenient method for preparing a large range of differently substituted sucrose molecules. We have successfully adapted this process to the etherification of other polysaccharides using $Pd(OAc)_2$ as catalyst and related work is in progress.

Experimental

Catalytic experiment

Sucrose was purchased from Riedel-de Haën, $Pd(OAc)_2$ (98%) and TPPTS (96%) from Aldrich; butadiene (99.5%) was obtained from Air Liquide.

In a typical experiment, the reaction was performed in a 150 ml stainless steel autoclave, equipped with a mechanical stirrer. Sucrose (4 g, 11.7 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol, 0.8%) and TPPTS (150 mg, 0.26 mmol) were introduced with solvent. The mixture was stirred for a few minutes to solubilise the catalyst. The autoclave was purged with argon, then frozen (−10 °C), and liquid butadiene (15–20 g, 280–370 mmol) added. The mixture was warmed to room temperature and heated to 80 °C. The pressure increased to 8 bar corresponding to the butadiene vapour pressure at that temperature. After the reaction, the autoclave was cooled, degassed and purged with argon. The solution was filtered (millipore 0.22 mm), to remove catalyst, then the solvents were evaporated *in vacuo* and the crude mixture weighted.

Analytical procedure

The reaction medium was analysed by gravimetric measurement, NMR, LSIMS and GC to determine the degree of substitution and the nature of the products. Prior to NMR and GC analysis, an aliquot of the reaction medium was derivatised. Typically, 500 mg of crude product was dissolved in pyridine (5 ml) and a catalytic amount of DMAP (dimethylaminopyridine) and 1.6 ml of Ac_2O were added. The solution was stirred at room temperature for 12 h then quenched with water (5 ml) and extracted with diethyl ether (5 ml). The organic phase was washed with 2 M HCl, saturated $NaHCO_3$ then saturated $CuSO_4$, dried over Na_2SO_4 and concentrated *in vacuo*.

Weight uptake measurements

The degree of substitution (DS), defined as the average number of octadienyl chain per sucrose entity, is proportional to the weight uptake. The molecular weight of the fully substituted sucrose should reach 1206 g mol^{-1} from an initial molecular weight of 342 g mol^{-1} for sucrose *i.e.*, complete alkylation would lead to a theoretical weight uptake of 250%. The weight uptake was determined after evaporation of the solvent, however, owing to the hydrophilic character of carbohydrate derivatives, some water could be present even after a long evaporation time and so we estimated the uncertainty of the value as 10%.

NMR analysis

^1H and ^{13}C NMR spectra were recorded on a Brüker AM 250 spectrometer (250 and 62.5 MHz, respectively) to determine the DS. After derivatisation with acetic anhydride of the reaction products, the signals corresponding to the acetate groups and to the ether groups at δ 2 and 1.5, respectively, were measured and correlated with the OAc/ether ratio. DS was calculated according to: $DS = 8/[(2I_1/3I_2) - 1/3]$, where I_1 and I_2 are the values obtained by integration of the δ 2 and 1.5 signals. This calculation takes into account only the hydroxyl groups substituted by C_8 chains; however these chains were shown to be predominant according to LSIMS analysis. An acceptable correlation was achieved with the two measurements.

Liquid secondary ionisation mass spectrometry (LSIMS)

The nature of the products was determined by LSIMS on a NERMEG R 10-10 type machine. Glycerol and thioglycerol were tested as matrices but in our case, *p*-nitrobenzyl alcohol in the presence of sodium acetate was found to be best and the corresponding sodium adducts $(M + Na)^+$ were analyzed. All sucrose derivatives (mono-, di-, tri-, tetra-ethers...) were detected under these conditions (except sucrose).

GC measurements

The conversion of sucrose was determined by GC analysis of the peracetylated product using a high temperature column [HT_5, SGE, 180–330 °C, 10 °C min^{-1} then 330–380 °C, 5 °C min^{-1}-t_R (sucrose) = 15 min].

Acknowledgements

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Clay-catalysed solventless synthesis of *trans*-chalcones

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trans-Chalcones have been obtained in good yields and selectivities following an environmentally friendly methodology by using montmorillonite KSF as a reusable heterogeneous catalyst.

Introduction

trans-Chalcones represent an important class of compounds employed as such for their interesting antineoplastic, spasmolytic, antibiotic, bacteriostatic and bactericidal properties[1] or, due to their chemical flexibility, as synthons for the production of five- and six-membered ring systems.[2]

Due to stringent and growing environmental regulations, the chemical industry needs the development of more eco-compatible synthetic methodologies and consequently a detailed re-examination of the most important synthetic processes.[3] To this purpose heterogeneous catalysis, which over recent years has received particular attention from both industrial and academic institutions, can play an important role, mainly due to its advantages from economic and environmental point of view (*i.e.* recycling of the catalyst, low corrosion, minimum execution time, waste minimisation, easy transport and disposal of catalysts).[4] An additional input towards the so-called ideal synthesis[5] is represented by the possibility to carry out the reaction in eco-compatible solvent (*i.e.* water) or better under solventless conditions. Since the revision of fundamental synthetic reactions under heterogeneous catalysis represents the subject of continuous investigation in our research group,[6] we have recently examined the synthesis of *trans*-chalcones under clay catalysis.

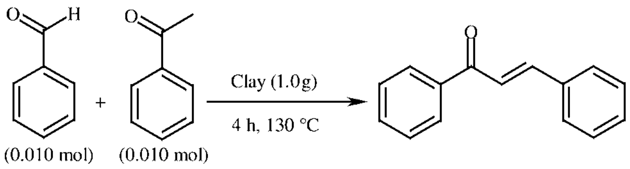
Under homogeneous conditions, these compounds are usually prepared by base or acid catalysed aldol condensation between aromatic aldehydes and ketones with stoichiometric amount of aqueous[7] or solid[8] sodium hydroxide, or catalytic amount of *p*-toluenesulfonic acid.[9]

Different acid and basic solid catalysts have been employed to synthesize *trans*-chalcones, in particular ion-exchanged mesoporous materials,[10] boric acid [11] or potassium hydroxide[12] impregnated silica gel, sulfonated charcoal[13] and hydrotalcites;[14] the microwave technique in the presence of a solid catalyst has been also utilised for production of the title compound;[9] moreover with this technique catalyst recycling is problematic, probably due to the catalyst structure modification by microwave.

Results and discussion

As anticipated, we decided to perform the synthesis of *trans*-chalcones over cheap and commercially available heterogeneous catalysts such as clays. To this end three different montmorillonites [KSF[15] (Fluka), K10[16] (Fluka) and STx-1[17] (Clay Source)], an hectorite [SHCa-1[18] (Clay Source)] a bentonite [Bieliaca[19] (Rudex)] and kaolin[20] (Aldrich)] were tested in the model reaction between benzaldehyde **1a** and acetophenone **2x** carried out under solventless condition at 130 °C for 4 h.

Table 1 *trans*-Chalcone synthesis catalysed by different clays



(0.010 mol) **1a** + (0.010 mol) **2x** → **3ax**

Entry	Catalyst	**3ax** Yield [selectivity[a]] (%)
1	None	0 [—]
2	Montmorillonite KSF	63 [95]
3	Montmorillonite K10	27 [97]
4	Montmorillonite STx-1	0 [—]
5	Hectorite SHCa-1	0 [—]
6	Bentonite Bieliaca	41 [92]
7	Kaolin	2 [96]

[a] (Yield of **3ax**/conversion of **2x**) × 100.

Green Context

Solvent minimisation can improve a process by reducing the problem of VOC emissions, and by reducing the volume required to carry out a process. This paper describes a solvent-free reaction, leading to very good yields of chalcones with excellent selectivity. The process involves heating with an acidic clay, which can afterwards be regenerated and reused. While the reaction itself is solvent-free, the isolation involves washing the catalyst with moderate amounts of ethanol. Nonetheless, the process represents a step towards solvent free processing, and has the potential to be adapted to run with a solventless isolation process.

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As emerges from Table 1, only acid clays, such as montmorillonites KSF, K10 and Bieliaca, (entries 2, 3 and 6) allowed the isolation of the product **3ax** in reasonable yields, whereas surprisingly the use of neutral (kaolin) or basic (montmorillonite STx1 and hectorite) catalysts leaded to the nearly complete recovery of the starting materials (entries 7, 4 and 5). Among the three active acid clays, montmorillonite KSF gave the best result affording the *trans*-chalcone in 63% yield and 95% selectivity. In all cases only the *Z* isomer was detected. To improve the process, we decided to vary both reaction time and catalyst amount.

At first, the model reaction over KSF catalyst was analysed comparing the concentration of reagent **2x** and product **3ax** *vs.* time (Fig. 1).

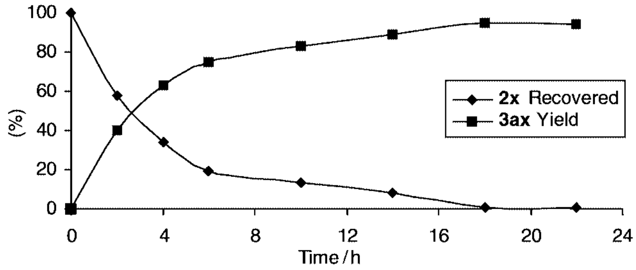


Fig. 1 Reactivity of banzaldehyde with acetophenone in the presence of montmorillonite KSF at 130 °C as a function of time.

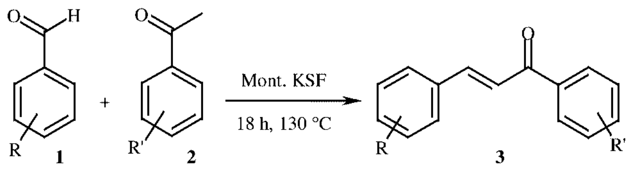
Results confirm that the maximum production of **3ax** occurs during the first 6 h (*ca*. 75% yield), then the reaction proceeds slowly and the yield reaches its maximum (*ca*. 95% yield) after 18 h.

Afterwards the effect of the catalyst amount was checked; to this end the same model reaction (0.010 mol each reagent) was carried out in the presence of 0.1 g, 0.5 g, 1.0 g and 2.0 g of montmorillonite KSF at 130 °C for 18 h; product **3ax** was obtained in 7%, 62%, 95% and 96% yield respectively. These data show that the best catalyst/reagents ratio was 1.0 g/ 0.010 mol.

To explore the general validity of this process, different *trans*-chalcones were synthesized by stirring at 130 °C for 18 h a mixture of the selected aromatic aldehyde (0.010 mol), the selected acetophenone (0.010 mol) and montmorillonite KSF (1.0 g); results are depicted in Table 2.

The reaction is of general applicability and other functionalities such as nitro, chloro, cyano, ether were preserved. It must be underlined that the reactivity is not affected by the nature of the substituents on both aromatic rings.

Table 2 Synthesis of variously substituted *trans*-chalcones



Entry		R		R′	**3** Yield [selectivity[a]] (%)
1	**1a**	H	**2x**	H	**3ax** 95 [95]
2	**1a**	H	**2y**	4-Me	**3ay** 87 [96]
3	**1b**	4-Cl	**2y**	4-Me	**3by** 80 [98]
4	**1c**	4-OMe	**2z**	4-Cl	**3cz** 82 [95]
5	**1d**	2-Cl	**2z**	4-Cl	**3dz** 90 [94]
6	**1e**	4-CN	**2x**	H	**3ex** 84 [97]
7	**1f**	4-NO_2	**2x**	H	**3fx** 83 [96]
8	**1g**	4-Ph	**2x**	H	**3gx** 80 [92]
9	**1e**	4-CN	**2y**	4-Me	**3ey** 95 [96]
10	**1e**	4-CN	**2z**	4-Cl	**3ez** 93 [98]

[a] (Yield of **3**/conversion of **2**) × 100.

Finally we faced the problem of catalyst recycling. After filtration, washing with methanol and heating at 100 °C overnight, the montmorillonite KSF was reused for four times showing a modest yield decrease only in the last two cycles (Reaction: 95%; 1st recycle: 93%; 2nd recycle: 94%; 3rd recycle: 81%; 4th recycle: 82%).

Conclusions

In conclusion, we have reported a new, effective and environmentally friendly methodology for the preparation of *trans*-chalcones; these compounds can be synthesized in high yield and excellent selectivity by using a commercial acid clay (montmorillonite KSF) and avoiding the use of any solvent. In addition the catalyst can be utilised at least five times.

Experimental

Typical procedure

Montmorillonite KSF (1.0 g), the selected benzaldehyde (0.010 mol) and the selected acetophenone (0.010 mol) were placed in a small autoclave and heated at 130 °C for 18 h. After cooling to room temperature, 95% ethanol (25 ml) was added, the mixture was filtered, the catalyst washed with hot 95% ethanol (25 ml) and the products crystallised from the same solvent. All the products gave mps and spectral data consistent with the reported data.

Acknowledgements

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15 Surface area: 15 ± 10 $m^2 g^{-1}$; surface acidity: 0.70 meq. $H^+ g^{-1}$ [determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD)]; chemical composition (average value): SiO_2 (54.0%), Al_2O_3 (17.0%), Fe_2O_3 (5.2%), CaO (1.5%), MgO (2.5%), Na_2O (0.4%), K_2O (1.5%).

16 Surface area: 200 ± 10 $m^2 g^{-1}$; surface acidity 0.65 meq H^+/g [determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD)]; chemical composition (average value): SiO_2 (73.0%), Al_2O_3 (14.0%), Fe_2O_3 (2.7%), CaO (0.2%), MgO (1.1%), Na_2O (0.6%), K_2O (1.9%).

17 Surface area: 84 ± 1 $m^2 g^{-1}$; surface acidity 0.27 meq. $H^+ g^{-1}$ [determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD)]; chemical composition (average value): SiO_2 (70.1%), Al_2O_3 (16.0%), TiO_2 (0.2%), Fe_2O_3 (0.7%), FeO (0.2%), CaO (1.6%), MgO (3.7%), Na_2O (0.3%), K_2O (0.1%).

18 Surface area: 63 ± 1 $m^2 g^{-1}$; surface acidity 0.21 meq. $H^+ g^{-1}$ [determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD)]; chemical composition (average value): SiO_2 (34.7%), Al_2O_3 (0.7%), TiO_2 (0.1%), FeO (0.3%), CaO (23.4%), MgO (15.3%), Na_2O (1.3%), K_2O (0.1%), Li_2O (2.2%).

19 Surface area: 63 ± 1 $m^2 g^{-1}$; surface acidity 0.21 meq. $H^+ g^{-1}$ [determined in our laboratory by temperature programmed Surface area: 205 ± 5 $m^2 g^{-1}$; surface acidity 0.77 meq. $H^+ g^{-1}$ [determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD)]; chemical composition (average value): SiO_2 (77.2%), Al_2O_3 (17.1%), TiO_2 (0.2%), Fe_2O_3 (1.7%), CaO (0.4%), MgO (3.0%), Na_2O (0.4%), K_2O (0.5%).

20 Chemical composition (average value): SiO_2 (47.5%), Al_2O_3 (37.8%), TiO_2 (0.04%), Fe_2O_3 (0.6%), CaO (0.06%), MgO (0.2%), Na_2O (0.1%), K_2O (1.1%).

Selective synthesis of 5-methyl-2-phenylpyridine from carbonyl compounds and ammonia over zeolite catalysts†

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The vapor-phase cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia was carried out over HZSM-5, Hβ and HY zeolites at 400 °C and 0.5 h^{-1} weight hour space velocity to synthesize 5-methyl-2-phenylpyridine. The cyclization activity follows the order: HY > Hβ > HZSM-5. The influence of catalyst modification with a metal ion, temperature, feed molar ratio, weight hour space velocity, and activity with time on stream parameters were studied. The maximum yield of 5-methyl-2-phenylpyridine was obtained over 3 wt% CoHY zeolite at 400 °C.

Introduction

Phenylpyridine and substituted phenylpyridines are useful intermediates in the synthesis of drugs, agrochemicals, herbicides, insecticides, desiccants, surfactant agents and anti-inflammatory agents.[1,2] They are widely used as ligands in co-ordination complex preparation. 2-Phenylpyridine is a starting material for BMS-232632 and it is a potent azapeptide HIV protease inhibitor that has shown high anti-HIV activity.[3] Traditionally phenylpyridines are synthesized by the arylation of pyridine and picolines with phenyllithium[4,5] and also by Grignard reactions.[6,7] Phenylpyridines were also photocatalytically synthesized from benzonitrile and ethylene in the presence of light using cobalt(I) complex as a catalyst. However these reactions are performed in homogeneous catalysis mode and they suffer from catalyst recovery and end up with tedious work up procedures. A Japanese patent by Shimizu *et al.* describes the synthesis of 6-methyl-2-phenylpyridine from acetophenone, acetone, formaldehyde and ammonia by aluminosilicate catalysts in vapor phase at 350–550 °C.[1] However, the catalysts are not zeolites and the yield of 6-methyl-2-phenylpyridine is only 50%. Zeolites with crystalline and uniform pore structure are proved to be efficient catalysts in acid-mediated reactions. The characteristics that make zeolites as attractive heterogeneous catalysts are their well-defined crystalline structure, a high internal surface area, uniform pores with one or two discrete sizes, the possibility of tuning acidity to a wide range, good thermal stability, shape selectivity and ease of separation. Many pyridine bases such as pyridine, picolines, lutidines and collidines have been synthesized from carbonyl compounds/alcohols with ammonia over zeolite catalysts.[8–14] However, no attempts have been made on the synthesis of large molecular size pyridine bases like phenylpyridine and substituted phenylpyridines. Recently large pore zeolites and mesoporous molecular sieve catalysts have been reported to be excellent catalysts especially for the synthesis of large molecules.[15–19] Earlier studies in our laboratory have also established that the combination of acidity, thermal stability and uniform pore structure of a molecular sieve catalyst provides a good opportunity for the synthesis of large size molecules such as 2-phenylpyridine and 2-methyl-6-phenylpyridine.[20–22] The present synthesis of 5-methyl-2-phenylpyridine from acetophenone, propionaldehyde, formaldehyde and ammonia over molecular sieve catalysts in the vapor phase, to the best of our knowledge, is the first such report.

Experimental

The HZSM-5 (30) zeolite was supplied by Conteka, Sweden, Hβ (20) from Sud-chemie, India and HY (2.6) zeolite from PQ Corporation, USA. The catalyst powder was pelletized, crushed and sieved into 2 mm sized granules. The required amount of metal nitrate in aqueous medium was taken onto the sized catalyst to modify the surface by impregnation followed by calcination in air at 400 °C for 4 h.

Acetophenone (99%) and formaldehyde (30% aqueous solution) (obtained from S. D. Fine Chem.-Ltd, India), propionaldehyde (97%) (from Lancaster, England) and methanol (99.85) (from E-Merck, India) were used in this study. The liquid feed is prepared in the molar ratio of 1:1:1:1 of acetophenone, propionaldehyde, formaldehyde and methanol. The methanol is used as a solvent to provide total miscibility of the feed. The vapor phase cyclization reaction was carried out using a continuous fixed bed Pyrex glass reactor of 20 mm internal diameter. 4 g of catalyst was used in the form of granules and placed in the middle of the reactor. The reactor was placed inside a temperature-controlled furnace with a thermo-

Green Context

This paper describes for the first time the direct synthesis of 5-methyl-2-phenylpyridine from the vapour phase reaction of acetophenone, propionaldehyde, formaldehyde and ammonia using zeolite catalysts. This remarkable multi-step reaction is not surprisingly not 100% selective but the yield of the desired pyridine is improved by the use of larger pore catalysts such as HY. Phenylpyridines are useful intermediates for example, in the preparation of the potent azapeptide HIV protease inhibitor BMS-232632. Their synthesis has traditionally induced acrylation reactions using organometallic reagents which result in high levels of hazardous waste. A single 'step' synthesis involving inexpensive substrates and a safe reusable catlyst is a very attractive option. *JHC*

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couple placed at the center of the catalyst bed for measuring the reaction temperature. The reaction mixture was fed from the top using a B. Brown (Germany) syringe pump. The product was cooled in a water-cooled (ice-cold) condenser, collected in a receiver and analyzed by gas chromatography (Chemito 3865) using 10% SE-30 on chromosorb HIWP packed column and products were confirmed by GC–MS and NMR spectroscopy. The product distribution at different time intervals is given in Tables 2–4.

Temperature programmed desorption (TPD) for ammonia experiments were carried out to measure the acidity of the catalyst as reported earlier.[21] In a typical run, a 0.150 g portion of the catalyst was placed in a quartz tubular reactor and heated at 400 °C under a nitrogen flow of 30 $cm^3 min^{-1}$ for 3 h and the reactor was then cooled to 25 °C and adsorption conducted at that temperature by exposing the sample to ammonia for 2 h. Physically adsorbed ammonia was removed by purging the sample with a nitrogen stream flowing at 30 $cm^3 min^{-1}$ for 1 h at 80 °C. The acid strength distribution was obtained by raising the catalyst temperature (10 °C min^{-1}) from 80 to 600 °C in a flow of nitrogen (10 $cm^3 min^{-1}$). The NH_3 gas evolved was quantified by gas chromatography using a thermal conductivity detector.

Results and discussion

Physicochemical properties

The frameworks of the modified zeolites were checked by X-ray diffraction and FTIR measurements and the crystallinity was found to be retained after modification. The surface areas of the modified zeolites were measured by the BET method and are listed in Table 1. The decrease in the surface area of the metal modified zeolites relative to the unmodified samples is due to the presence of metal ions and oxide species in the cavities of the zeolite. The surface area of cobalt metal-modified HY zeolite decreases with an increased amount of cobalt. The acidity of the zeolites and modified zeolites were measured by the method of temperature programmed desorption of ammonia and the values are given in Table 1. The total acidity of the catalysts followed the order: CuHY < PbHY < MnHY < CrHY < ZnHY < CoHY < HY < FeHY < LaHY. As reported earlier, HY catalyst modified by rare earth cations such as La, showed higher acidity than unmodified zeolites.[23,24]

Table 1 Physical characteristics of various zeolite catalysts

Catalyst	SiO_2/Al_2O_3	Acidity/ mmol g^{-1}	Surface area/$m^2 g^{-1}$
HZSM-5	30	1.73	310.0
Hβ	20	1.92	435.8
HY	2.6	2.83	457.2
3-wt % metal ion on HY zeolite			
Cr		2.09	411.4
Mn		1.98	449.0
Fe		3.16	377.3
Co		2.46	447.0
Cu		1.17	432.2
Zn		2.12	427.8
Pb		1.55	448.3
La		3.41	355.7
Co loading on HY zeolite (wt %)			
1			450.8
3			447.5
5			428.0
10			348.4

Catalytic activity

The vapor-phase cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia was carried out over zeolites HZSM-5, Hβ, HY and SiO_2-Al_2O_3 at 400 °C with 0.5 h^{-1} weight hour space velocity to synthesize 5-methyl-2-phenylpyridine and the results are given in Table 2. HZSM-5, Hβ, HY and SiO_2-Al_2O_3 showed conversion of acetophenone of 85.0, 87.0, 99.8 and 96.4% respectively. The yields of 5-methyl-2-phenylpyridine for HZSM-5, Hβ, HY and SiO_2-Al_2O_3 are 23.6, 29.1, 37.9 and 25.4%, respectively. The cyclization activity follows the order: HY > Hβ > SiO_2-Al_2O_3 > HZSM-5. Even though good conversion level on the HZSM-5 catalyst is seen, the low yield of the product observed may be due to inaccessibility or slower diffusion of the product 5-methyl-2-phenylpyridine to diffuse through the pores of ZSM-5 zeolite (5.4 Å). The lower yield of 5-methyl-2-phenylpyridine over Hβ compared to HY is due to secondary reactions and also may be due to slower diffusion of the product through the pores of different geometry (pore size 7.6 × 6.4 and 5.5 × 5.5 Å).[25,26] It is seen that higher yields of 5-methyl-2-phenylpyridine were obtained over zeolites where there is no diffusion limitation of the product. This is also supported by our earlier studies on the synthesis of 2-phenylpyridine[22] and 2-methyl-6-phenylpyridine.[20,21] The pore size of the catalyst must be accessible to reactant and product molecules in order for the reaction to occur.

The reaction was carried out over 3 wt% Cr, Mn, Fe, Co, Cu, Zn, Pb and La metal ion-modified HY zeolites at 400 °C with 0.5 h^{-1} weight hour space velocity and the results are given in Table 3. The cyclization activity for 5-methyl-2-phenypyridine followed the order: CoHY > CuHY ≈ ZnHY > CrHY > MnHY > FeHY > PbHY > LaHY. There is no drastic change in the catalytic activity observed upon varying the metal ion and this may be attributed to the presence of several competitive and parallel reactions in a multi-reactant process. The high acidity of LaHY enhances the formation of side products so showing low selectivity and yield of 5-methyl-2-phenylpyridine (Fig. 1). It is observed that mildly acidic Co, Pb, Cu and Zn modified zeolites

Table 2 Synthesis of 5-methyl-2-phenylpyridine from acetophenone, propionaldehyde, formaldehyde and ammonia over various catalysts[a]

		Product distribution (%)[b]					
Catalyst	Acetophenone conversion (%)	5,2-MPP	2,6-MPP	2-PP	3,5-Lutidine	Other alkylpyridines	Others
HZSM-5 (30)	85.0	23.6	0.9	0.2	32.3	15.0	13.0
Hβ	87.0	29.1	1.2	0.8	14.3	10.8	30.8
HY	99.8	37.9	0.2	0.1	36.0	9.3	21.5
SiO_2-Al_2O_3	96.4	25.4	7.9	3.7	11.2	8.5	39.7

[a] Feed: acetophenone–propionaldehyde–formaldehyde–methanol–ammonia = 1:1:1:1:5 (mole ratio); reaction temperature: 400 °C; weight hour space velocity: 0.5 h^{-1}; time on stream: 4 h. [b] 5,2-MPP = 5-methyl-2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 2-PP = 2-phenylpyridine; other alkylpyridines = pyridine, isomers of picolines, lutidine and collidine; others = isomeric mono- and di-alkylphenylpyridines, 2,6-diphenylpyridine and aldolization products.

Table 3 Synthesis of 5-methyl-2-phenylpyridine over various metal ion modified-HY zeolite[a]

Catalyst	Acetopenone conversion (%)	Product distribution (wt%)[b]					Selectivity of 5,2-MPP
		5,2-MPP	2,6-MPP	2-PP	3,5-Lutidine	Others	
CrHY	93.0	43.4	2.8	0.1	18.7	28.0	46.7
MnHY	93.3	43.3	2.6	—	23.9	23.5	46.4
FeHY	96.2	44.2	3.1	0.9	19.8	28.2	45.9
CoHY	96.0	48.5	2.1	0.7	16.7	28.0	50.5
CuHY	92.8	44.3	3.0	—	24.6	20.9	47.7
ZnHY	98.7	47.1	2.5	—	22.8	26.3	47.7
LaHY	97.9	34.5	0.2	0.4	15.1	47.7	35.2
PbHY	95.6	43.5	2.9	1.6	24.2	23.4	45.5

[a] Feed: acetophenone: propionaldehyde–formaldehyde–methanol–ammonia = 1 : 1 : 1 : 1 : 5 (mole ratio); reaction temperature: 400 °C; Weight hour space velocity = 0.5 h^{-1}. [b] 5,2-MPP = 5-methyl-2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 2-PP = 2-phenylpyridine; others = pyridine, isomers of picolines, lutidine and collidine, isomeric mono- and di-alkylphenylpyridines, 2,6-diphenylpyridine and aldolization products.

led to a slightly higher yield of 5-methyl-2-phenylpyridine. The maximum yield of 5-methyl-2-phenylpyridine was obtained on cobalt metal-modified HY catalyst. Earlier reports on the synthesis of pyridine, picolines and lutidines from carbonyl compounds and ammonia also reveal that cobalt-modified zeolites are active for this type of aminocyclization reaction.[27] In order to gain more insight into the reaction, process parameters such as effect of loading of cobalt on HY zeolite, variation of molar ratio of the reactants, weight hour space velocity and product distribution with time on stream studies, have been studied.

The reaction was studied in the temperature range 300–450 °C for the cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia over 3 wt% CoHY catalyst and the results are given in Table 4. The maximum yield of 5-methyl-2-phenylpyridine was observed at 400 °C. Below 400 °C the conversion of acetophenone and the yield of the product is very low. This may be due to the adsorption of ammonia at lower temperatures, thus blocking the active sites for the reaction to proceed. As the temperature was increased, ammonia starts desorbing making the active sites available for the reaction to occur. Further increase in the temperature above 400 °C decreases the conversion levels and yield of 5-methyl-2-phenylpyridine possibly due to coke formation.

The reaction was studied over 1–10 wt% cobalt ion containing HY zeolite and the results are shown in Fig. 2(a). The optimum percentage of loading was found to be 3 wt%. Further increase in the amount of cobalt decreases the conversion of acetophenone and yield of the 5-methyl-2-phenylpyridine owing to the fall in surface area of the catalyst.

The effect of reactant molar ratio for the synthesis of 5-methyl-2-phenylpyridine was studied from 0.5 : 1 to 2 : 1 of acetophenone to propionaldehyde whilst retaining the amounts of formaldehyde and ammonia at a constant level. The maximum yield of 5-methyl-2-phenylpyridine was obtained at a 1 : 1 molar ratio of acetophenone to propionaldehyde as shown in Fig.2(b). An increase of either of the reactants leads to a decrease in the yield of 5-methyl-2-phenylpyridine. An excess of propionaldehyde in the feed increases the formation of pyridine and isomers of picolines and lutidine compounds resulting in a low yield of 5-methyl-2-phenylpyridine. On the other hand, an excess of acetophenone in the feed also decreases the yield of 5-methyl-2-phenylpyridine. This is due to non-availability of required number of propionaldehyde molecules for the cyclization reaction to occur. The formation of aldolization products of acetophenone were also increased.

Variation of weight hour space velocity (WHSV) on the aminocyclization of acetophenone, propionaldehyde, formaldehyde and ammonia was studied in the range 0.25–1 h^{-1} and the results are given in Fig. 2(c). The yield of 5-methyl-2-phenylpyridine decreased with an increase of WHSV due to the decrease in the contact time between reactants and active sites of the catalyst. The maximum yield of 5-methyl-2-phenylpyridine was obtained at a WHSV of 0.5 h^{-1}.

The effect of time on stream on the cyclization reaction was studied for a duration of 10 h over 3 wt% CoHY catalyst at 400 °C and 0.5 h^{-1} weight hour space velocity and the results are given in Fig. 2(d). The catalytic activity was found to be

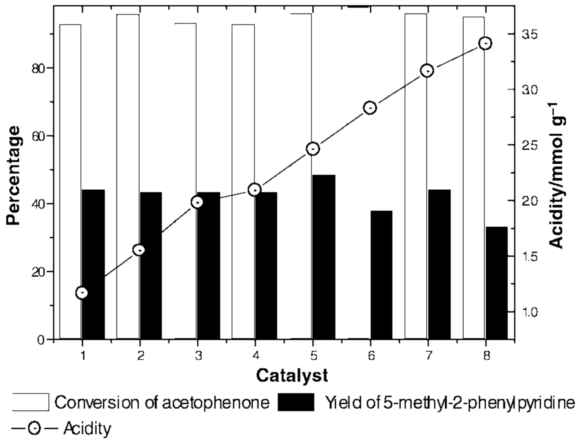
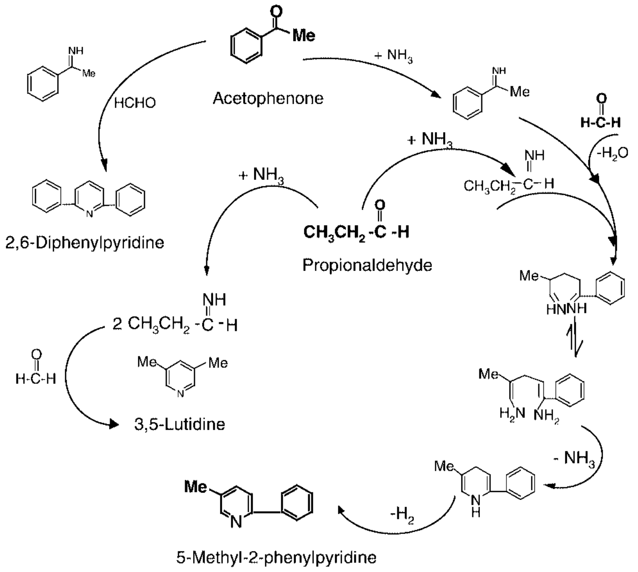


Fig. 1 Effect of acidity of metal ion modified-HY zeolites on the synthesis of 5-methyl-2-phenylpyridine: (1) Cu, (2) Pb, (3) Mn, (4) Cr, (5) Co, (6) HY, (7) Fe (8) La. Feed: acetophenone–propionaldehyde–formaldehyde–methanol–ammonia = 1 : 1 : 1 : 1 : 5 (mole ratio); reaction temperature: 400 °C: weight hour space velocity: 0.5 h^{-1}; time on stream: 4 h.



Scheme 1 A plausible reaction mechanism for the formation of various products during the synthesis of 5-methyl-2-phenylpyridine.

Table 4 Effect of temperature on the synthesis of 5-methyl-2-phenylpyridine over 3 wt% CoHY zeolite[a]

Reaction temperature/°C	TOS/h	Acetophenone conversion (%)	Product distribution (%)[b] 5,2-MPP	2,6-MPP	2-PP	3,5-Lutidine	Others
300	2	67.6	25.8	5.0	2.9	6.2	27.7
	4	50.0	15.2	2.9	2.3	4.6	25.0
350	1	56.4	15.7	3.1	3.0	4.4	30.2
	4	55.0	18.4	2.0	3.0	5.8	25.8
400	4	96.0	48.5	2.1	0.7	16.7	28.0
450	1	57.9	17.7	2.8	3.1	4.5	29.8
	4	49.8	16.2	2.5	0.7	5.3	25.1

[a] Feed = acetophenone–propionaldehyde–formaldehyde–methanol–ammonia = 1 : 1 : 1 : 1 : 5 (mole ratio); Weight hour space velocity = 0.5 h^{-1}. [b] 5,2-MPP = 5-methyl-2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 2-PP = 2-phenylpyridine; others = pyridine, isomers of picolines, lutidine and collidine, isomeric mono- and di-alkylphenylpyridines, 2,6-diphenylpyridine and aldolization products. TOS = Time on stream.

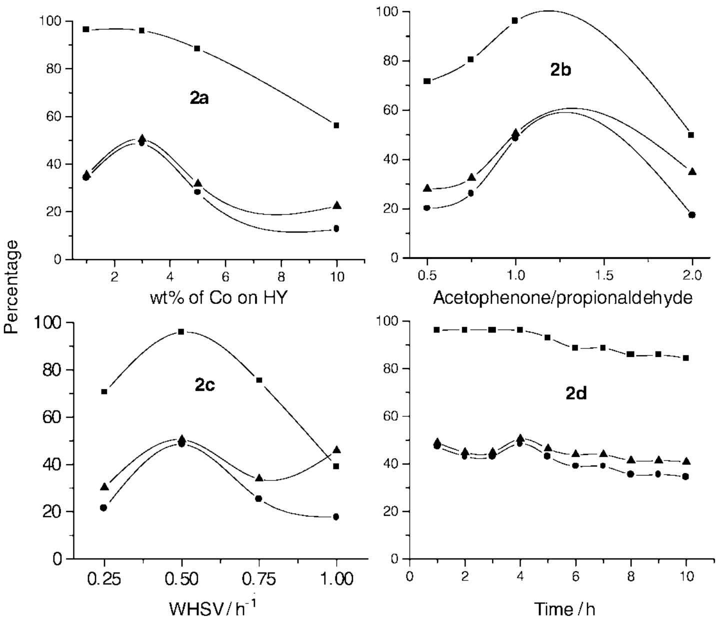


Fig. 2 Effect of reaction parameters on the synthesis of 5-methyl-2-phenylpyridine. (a) Effect of cobalt loading on HY zeolite. (b) Effect of feed mole ratio of acetophenone to propionaldehyde. (c) Effect of weight hour space velocity (WHSV). (d) Effect of time on stream. (■) conversion of acetophenone; (●) yield of 5-methyl-2-phenylpyridine; (▲) selectivity of 5-methyl-2-phenylpyridine.

constant for the first 5 h, with subsequent deactivation probably due to coke formation.

Reaction mechanism

A plausible scheme for the reaction of acetophenone, propionaldehyde, formaldehyde and ammonia over zeolite catalyst is given in Scheme 1. Acetophenone and propionaldehyde react with ammonia forming the corresponding imines. Thus formed, two molecules of imine react with formaldehyde resulting cyclization and dehydrogenation, which leads to the formation of 5-methyl-2-phenylpyridine. The formation of pyridine, picolines and lutidines during the reaction of propionaldehyde, formaldehyde and ammonia has been reported earlier.[14]

Conclusions

Vapor phase cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia over HZSM-5, Hβ and HY zeolites and SiO_2-Al_2O_3 involves multi-step reactions, which leads to the formation of 5-methyl-2-phenylpyridine as the major product and isomeric substituted phenylpyridines, pyridine, picolines and lutidines *etc.* as by-products. The conversion levels of reactants and yield of 5-methyl-2-phenylpyridine increased with pore size of the catalysts. The large pore size of the HY zeolite offers no constraints for the diffusion of the product and gives rise to high activity compared to the medium pore HZSM-5 catalyst. The maximum yield of 5-methyl-2-phenylpyridine was obtained over medium acidic 3 wt% CoHY zeolite at 400 °C. The high acidity/temperatures employed result in catalyst deactivation.

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A green route to the synthesis of azo compounds

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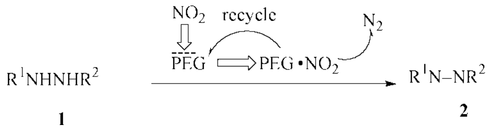
Polyethylene glycol (PEG, average molecular weight 400) was used as an absorbent for NO_2, the absorptivity was found to reach up to 97%. PEG·NO_2, the resulting absorbent product, proved to be a very efficient, clean and moderate oxidant, It can convert hydrazo derivatives **1** to the corresponding azo compounds **2** for the first time. The spent PEG can be recovered and recycled after the oxidation process.

The removal of NO_2 in gaseous waste products, discharged from nitric acid towers, power plants, or chemical reactors using nitric acids, is important due to stringent environmental restrictions regarding pollutant emissions. The treatment of nitrogen oxides has long been studied by many chemists. One of the possible approaches of the utilization of this compound may be based upon its medium oxidisability. However, as an oxidizing agent, NO_2 is inconvenient because of its low selectivity and gaseous state.[1] We now report that PEG can absorb NO_2 efficiently to form a new complex PEG·NO_2, which liberates NO_2 gradually in the course of reaction with other organic compounds. The infrared spectra of PEG and PEG·NO_2 were compared. ν_{max}/cm^{-1} 3430 (OH, PEG); 3420(OH, PEG·NO_2); 1108(C–O–C, PEG); 1083 (C–O–C, PEG·NO_2); 1650,1350,825,760 (ONO_2, PEG·NO_2). This complex proves to be a mild and selective oxidizing agent to convert hydrazo derivatives **1** to the corresponding azo compounds **2** in good yield under mild conditions (Scheme 1).



Scheme 1

Azo compounds have been utilized as dyes, analytical reagents, and as materials for non-linear optics and for storage optics information in laser dishes.[2] Recently, many noteworthy studies have shown that azo compounds possess excellent optic memory and photoelectric properties.[3] They have long played a significant role in the development of mechanistic and synthetic organic chemistry.[4] The preparation of azo compounds has been described in many references.[5] Generally, azo compounds are synthesized by diazo coupling or oxidising hydrazine using *N*-bromosuccinimide (NBS), potassium permanganate or fuming nitric acid.[6] Industrial chemists are especially interested in conducting oxidations in a simple way which avoids expensive reagents and solvents, and tedious work-up wherever possible. Fuming nitric acid can be employed as a relatively economical oxidant to convert hydrazine to azo compounds, but the evolution of large amounts of nitrogen oxides causes air pollution, and control of the reaction temperature is a major cost in industrialized manufacturing.[6a] The introduction of new methods, inexpensive reagents and environmentally friendly conditions for such functional groups transformations is still in demand. PEG can absorb NO_2 efficiently to form PEG·NO_2, The absorption efficiency of NO_2, which was determined by the Griess–Saltzman' method,[7] was found to reach up to 97% (Table 1). The concentration of NO_2 in PEG was 10.53 mmol g^{-1}, as determined by reacting PEG·NO_2 with an excess of aqueous sodium hydroxide and then back titrating with hydrochloric acid.[8] PEG is able to absorb NO_2 efficiently and the absorbent product PEG·NO_2 can be used as an oxidant to oxidize hydrazo derivatives to the corresponding azo derivatives in good yield under mild conditions for the first time (Table 2).

In order to optimize the reaction conditions, the effects of PEG, the reaction temperature and the mole ratio of starting materials were studied, and the tail gases of the reaction process were analyzed.

In the absence of PEG the reaction of nitrogen oxides proceeds vigorously at 0 °C to give low yields of azo compounds with aromatic nitration being a side reaction. For PEG·NO_2 the best temperature for reaction was within 25–35 °C. Below 25 °C, oxidation of the starting material was

Green Context

The efficient removal of pollutants in a way that enables their utilisation is a valuable application and represents a good example of clean technology and green chemistry. NO_2 is a major pollutant and while there are several methods for its capture an attractive option is to reduce it to environmentally benign N_2 in a constructive way. This paper brings together a new form of NO_2 capture with a valuable application for the trapped compound as an oxidant. PEG proves to have an extremely high capacity for NO_2 thus representing excellent mass efficiency. The resulting PEG·NO_2 proves to be a very good oxidant for hydrazo derivatives giving the corresponding azo compounds which have numerous applications in areas including dyes and materials for non-linear optics. Thus we have an efficient NO_2 trap leading to a valuable reagent with full recycle capability. ***JHC***

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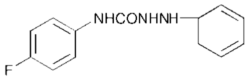
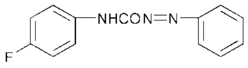
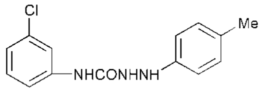
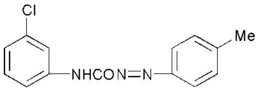
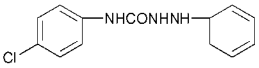
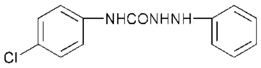
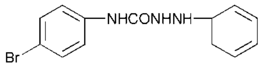
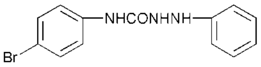
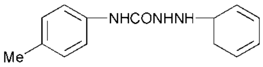
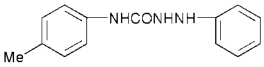
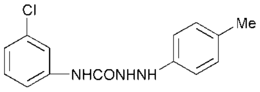
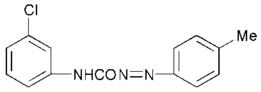
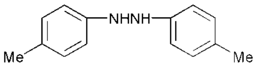
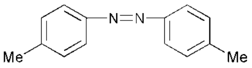
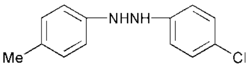
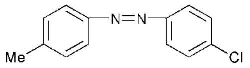
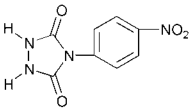
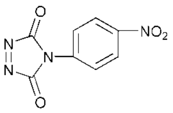
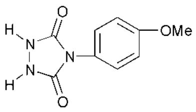
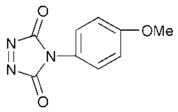
Table 1 The absorptivity of PEG towards NO_2

Flow velocity/L min^{-1}	Conc. of NO_2/mg m^{-3}								
	Tower (III)		Tower (IV)		Tower (V)		Absorptivity (%)		
	Inlet	Outlet	Inlet	Outlet	Inlet	Outlet	III	(III + IV)	(III + IV + **V**)
0.4	631123	62914	62914	8807	8807	840	90.0	99.4	99.9
0.6	258605	72405	72405	8497	8497	1140	72.0	88.0	99.4
0.8	116953	37425	37425	11110	11110	468	68.0	90.5	99.6
1.0	213047	72653	72653	12977	12977	1420	65.9	93.9	99.3
2.0	140878	61144	61144	12814	12814	1743	57.0	90.9	98.7
3.0	151221	64756	64756	12655	12655	1823	57.0	91.6	98.8
4.0	117712	46910	46910	10496	10496	2943	60.2	91.1	97.5
5.0	138989	61789	61789	19575	19575	2029	56.5	85.9	97.9
6.0	91892	39315	39315	10311	10311	2429	57.2	88.8	97.3
7.0	128224	60491	60491	12519	12519	3556	52.8	90.2	97.2

Table 2 Transformation of –NHNH– to –N=N– by PEG·NO_2

Entry	Substrate[a]	Time/min	Product[b]	Yield (%)[c]
a		25		92
b		20		90
c		25		88
d		30		90
e		20		85
f		25		93
g	$Cl_3CCH_2O_2CNHNHCO_2CH_2CCl_3$	25	$Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$	95
h	$EtO_2CNHNHCO_2Et$	20	$EtO_2CN{=}NCO_2Et$	92
i	$MeO_2CNHNHCO_2Me$	30	$MeO_2CN{=}NCO_2Me$	85
j		35		75
k		30		80
l		20		75
m		25		86

[a] All substrates were prepared by known literature procedures. [b] All known products were fully characterized by comparison of their mp, IR and ^1H NMR spectra with those of authentic samples. [c] Isolated yield based on the starting compounds **1**.

very slow and almost no product was obtained while above 45 °C, the yield decreased since NO_2 was desorbed from PEG and was not consumed efficiently. The optimum mole ratio of **1** to PEG·NO_2 was 1 : 2. No overoxidation product was observed with the use of a large excess of PEG·NO_2. This shows that PEG·NO_2 is a mild oxidant. Of interest, the tail gas, which was analyzed using a GC-9A gas chromatograph, was found to be composed of N_2 and NO in a ratio of 296 : 1 showing there was very little secondary pollution. PEG·NO_2 is thus an environmentally friendly oxidizing agent. The PEG can be recovered and recycled after the oxidation process.

In conclusion, we have developed an efficient, rapid and inexpensive methodology for the oxidation of hydrazo, hydrazide semicarbazide, and urazole derivatives to the corresponding azo compounds in excellent yields for the first time. PEG is a good carrier of NO_2 which can be recycled. PEG·NO_2 can be employed as an efficient, rapid inexpensive and environmentally friendly oxidizing agent to convert compounds containing

–NHNH– groups to azo compounds. Because the tail gas of the oxidation reaction was essentially pure N_2 and since the PEG can be regenerated by dehydration *in vacuo*, the reaction can be considered as 'green.' Studies in this field are also significant in terms of the treatment and utilization of waste gas NO_2. An attempt to establish a complete view of the reaction mechanism of the oxidation reactions is in progress.

Experimental

Melting points were determined with a Kofler micro melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet AVATAR 360 FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were measured on a Varian FT-80A spectrometer using TMS as internal standard and $CDCl_3$ as solvent. MS spectra were taken on a VGZAB-HS spectrometer. Elemental analyses were performed on an Elementar Vario EL elemental analyzer. The content of NO_2 was measured by Lombdar-17 UV spectrophotometer.

Preparation of PEG·NO_2

A gas stream containing NO_2 was obtained by drying and oxidising the feed gas NO_x (as soon as NO is contacted with air it is converted into NO_2), which was produced by the reaction of sodium nitrite with sulfuric acid (0.5 mol L^{-1}). The process of drying and oxidation were achieved by passing the NO_x flow through a sulfuric acid tower (I) and oxidizing column (II), which was packed with oxide sand (CrO_3: sand = 1:20) to ensure the conversion of NO to NO_2. In three connected absorbing towers III–V, three-stage absorption) [900 mm × 20 mm (i.d.)] packed with 3 × 3 mm stainless-steel Pall rings, the absorption was performed by spraying PEG from the top of the columns while introducing NO_2 from the bottom of the columns. The feed and effluent gas contents were determined on the basis of the method of Griess–Saltzman. The absorption process of PEG with NO_2 was conducted at ambient temperature and normal pressure. The liquid velocity of PEG was 5 ml $min.^{-1}$ As absorption proceeds the PEG changes from colorless to blue and finally to orange. PEG·NO_2, an orange liquid, is a stable, mild and efficient oxidizing agent.

Preparation of azo compounds (general procedure)

Hydrazo derivatives (10 mmol) and PEG·NO_2(1.9 g, 20 mmol) were stirred at 35 °C. After 25–35 min, the solution changed from yellow to orange and then orange–red. Cold water (20 ml) was then added slowly and the flocculent precipitate of the azo compound collected, washed with water and dried *in vacuo*; the products were obtained in excellent yield. Water was removed from the solution under reduced pressure, and the residual PEG was pure enough to recycle.

Acknowledgement

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Complexants for the clathration mediated synthesis of the antibiotic cephradine

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Enzymatic synthesis of cephalosporins is hampered by secondary hydrolysis and by complicated down-stream processing. Instantaneous removal of cephalosporin product by clathration, using an efficient and selective complexing agent, offers an attractive opportunity to tackle these problems. A series of benzene derivatives that form clathrate-type complexes with the cephalosporin antibiotics was subjected to efficiency measurements with Cephradine and enzyme inhibition studies. The best results for the antibiotic Cephradine were obtained with methyl 2-aminobenzoate, 2-hydroxybiphenyl and methyl 4-hydroxybenzoate. These three compounds are environmentally and toxicologically fully acceptable for application in a 'green' process.

Introduction

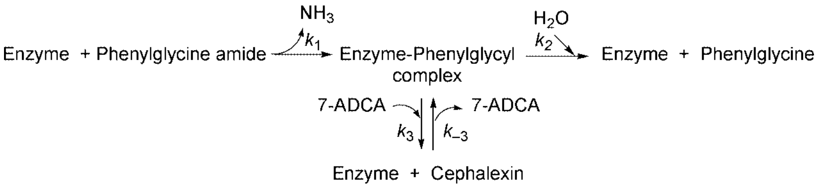
The enzymatic synthesis of cephalosporins forms a challenging new development for the manufacture of these antibiotics from a β-lactam nucleus and a D-amino acid side chain.[1] The enzymatic synthesis offers interesting possibilities for improvement of the processes used for the preparation of the cephalosporins. Another, attractive aspect of the enzymatic synthesis is the possibility to reduce the environmental impact of the processes for the manufacture of these antibiotics.[2] Introduction of biocatalysis will contribute enormously to the greening of the chemistry needed for the production of these important antibiotics. This development is fully in line with the global trend in the fine-chemical industry.[3]

A suitable biocatalyst for the coupling of nucleus and side chain is penicillin G acylase. Since the equilibrium constant of this thermodynamic coupling is extremely low,[4] the coupling has to be performed in a kinetic fashion using an activated precursor of the side chain in order to obtain a reasonable conversion to the product. A severe problem of this kinetic enzymatic synthesis of cephalosporins from the β-lactam nucleus and the ester or amide derivative of the side chain is hydrolysis of side chain and product, as is depicted for Cephalexin in Scheme 1.[5,6] In the first step phenylglycine amide is converted into its complex with the enzyme (k_1), which is accompanied by liberation of ammonia. The enzyme–phenylglycyl complex can undergo either hydrolysis with water (k_2) resulting in the formation of phenylglycine or reaction with the β-lactam nucleus 7-ADCA (k_3) to give Cephalexin. The cleavage of Cephalexin (k_{-3}) reverts to the enzyme–phenylglycyl complex and 7-ADCA. The competing reaction of the thus obtained enzyme–phenylglycyl complex with water leads to a loss of product and is often referred to as *secondary hydrolysis*.

Due to hydrolysis reactions the yield of the kinetic enzymatic coupling of nucleus and side chain is very low.[7] The unwanted hydrolysis can in principle be suppressed using a solvent other than water, which is, however, neither possible in real practice, nor desirable from an environmental point of view. In an

Green Context

The enzymatic synthesis of cephalosporins is an important process which is hampered by hydrolysis of the side chain in the aqueous environment. This paper describes the use of a series of benign clathrates, which efficiently remove the product from the aqueous phase as it is produced, minimising the extent of the hydrolysis, and making significant improvements in the overall process. The best clathrates remove the product very efficiently, and are of low toxicological impact. This work helps to make feasible a low energy, simple synthesis of an important group of compounds. ***DJM***



Scheme 1 Enzymatic synthesis of Cephalexin.

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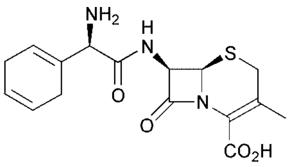
alternative manner to avoid secondary hydrolysis the cephalosporin product can be removed from the aqueous reaction mixture. Two techniques for the removal of Cephalexin from aqueous solutions are reported, *viz.* adsorption using amberlite XAD[8] and extraction using an aqueous two-phase system.[9] However, neither of these techniques is selective and consequently the starting materials are also withdrawn from the reaction mixture. In contrast to the aforementioned techniques, clathration of cephalosporins with a complexing agent such as β-naphthol is highly selective.[10] Hence, clathration of cephalosporins during the enzymatic synthesis may be suitable to tackle the problem of secondary hydrolysis. In addition, clathration of cephalosporins may be an elegant method to facilitate down-stream processing as the precipitated clathrate can be readily filtered off from the rather complex reaction mixture. The application of *in situ* clathration during the enzymatic synthesis of cephalosporins has been reported previously.[11] The beneficial effect of clathration with naphthalene-derived complexants on the product yield during the enzymatic synthesis of Cephalexin, has also been described in a quantitative manner.[12] Several requirements have to be fulfilled by a complexing agent before application during the enzymatic synthesis of cephalosporins becomes feasible. First, the clathration process must be sufficiently effective under the conditions used for the enzymatic coupling. Second, the complexing agent used must not (irreversibly) inactivate the enzyme. And third, preferably the complexing agent must be non-toxic. Despite the fact that by decomplexation, which is done by acidic or basic hydrolysis of the complex, extraction of the complexing agent followed by neutralisation of the resulting concentrated aqueous solution of cephalosporin, the complexing agent can be completely removed from the final product, the use of a toxic compound, *e.g.* β-naphthol, in a 'green' enzymatic process is not desirable. This paper describes a study of several non-toxic complexants for the cephalosporin antibiotic Cephradine with regard to complexation efficiency and enzyme inhibition.



Cephradine

Results

The beneficial effect of *in situ* clathration has been clearly demonstrated for the enzymatic synthesis of Cephalexin.[12] However, the toxicity of the complexing agent has not been taken into account yet. Although the complexing agent can be completely removed from the final product it is desirable to use a non-toxic complexing agent in a 'green' enzymatic process. The naphthalene-derived complexants do not meet this requirement. The benzene derivatives that were previously identified as complexing agents for Cephradine,[13] offer interesting prospects as several of them are used as preservatives in various food products. Such complexants are environmentally and toxicologically fully acceptable and according to their R classification, *i.e.* the risk of a substance in case of a particular exposure such as *via* skin, eyes, inhalation or swallowing, they have a toxicity index similar to other commonly used preservatives. Taking into account the complexing capacity and the favourable toxicity index the series of benzene derivatives listed in Table 1 were selected for the efficiency study in the enzymatic synthesis of Cephradine. These compounds were subjected to efficiency measurements under conditions that resemble those of the enzymatic synthesis of Cephradine, *viz.* pH = 7.2, *T* = 5 °C. The residual concentration of Cephradine was measured 90 min after the addition of the complexing agent. The results obtained for the most effective complexants under the just mentioned conditions are collected in Table 2. The other compounds of Table 1 were not effective at all under the desired conditions and are therefore of no interest for the removal of the antibiotic from aqueous reaction mixtures. For an acceptable complexant the residual concentration of antibiotic should be below 10 mM, as below this residual concentration the impact of complexation on the yield of the enzymatic synthesis becomes significant.[12] Five compounds listed in Table 2 met this criterion, *viz.* entries 1, 2, 6, 7, and 8. These five compounds were investigated in enzyme inhibition experiments using Assemblase[14] as the biocatalyst.[16]

Table 1 The compounds tested in efficiency measurements with Cephradine

o-Toluic acid
4-Aminoacetophenone
Methyl 2,4-dihydroxybenzoate
Methyl *p*-toluate
Recorcinol
3,4,5-Trihydroxybenzoic acid
2-Aminobenzamide
Pyrogallol
Acetophenone
Methyl 3-aminobenzoate
4-Methoxyphenol
2-Methoxyacetophenone
2,4-Dihydroxybenzoic acid
Benzoic acid
4-Methylacetophenone
3,5-Dihydroxybenzoic acid
Methyl *m*-toluate
Catechol
Methyl 3,5-dihydroxybenzoate
2-Aminobenzoic acid
Hydroquinone
Methyl 3,4,5-trihydroxybenzoate
Methyl 2-aminobenzoate
Phloroglucinol
2-Hydroxyacetophenone
Methyl 4-aminobenzoate
2-Hydroxybiphenyl
2-Methylacetophenone
3,4-Dihydroxybenzoic acid
Vanillin

In these studies the activity of the enzyme in the presence of a complexing agent was compared with that in the absence of complexing agent. The rate of hydrolysis of D-phenylglycine amide (the side chain precursor of Cephalexin) was taken as a measure for the enzyme activity. Three types of experiments were performed in order to obtain information about both reversible inhibition and inactivation (irreversible inhibition) of a complexing agent.

(i) Activity measurement in the presence of complexing agent.

(ii) Incubation of the enzyme with a complexing agent for 16.5 h, then the Assemblase was thoroughly washed with water and the activity was measured in the absence of complexing agent.

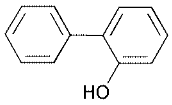
(iii) Incubation of enzyme with complexing agent for 16.5 h, after washing of the Assemblase with water the activity was measured in the presence of complexing agent.

The activity measured in experiment (i) was in all cases lower than the activity of Assemblase in the absence of complexant. However, from experiment (i) it cannot be ascertained whether the lower activity is due to reversible inhibition or inactivation (irreversible inhibition) by the complexant. Experiment (ii) indicates whether a complexant inactivates Assemblase. When after thorough washing the activity of Assemblase in the

Table 2 The residual concentration of Cephradine (pH = 7.2 and *T* = 5 °C) using benzene derivatives as complexants

Entry	Complexant	[Cephradine]/mM
1	2-Aminobenzoic acid	6.6
2	Methyl 2-aminobenzoate	3.7
3	2-Aminobenzamide	16
4	2-Methoxyacetophenone	15
5	4-Aminoacetophenone	16
6	2-Hydroxybiphenyl	1.3
7	Methyl 4-hydroxybenzoate	5.5
8	Methyl 3-hydroxybenzoate	6.9
9	Methyl 3,5-dihydroxybenzoate	14

absence of the complexant is not equal to the activity of fresh Assemblase this points to irreversible inhibition by the complexant. If this is the case then the complexing agent is not suitable for use during the enzymatic synthesis. In case no irreversible inhibition takes place, the activity of Assemblase after long-lasting (16.5 h) exposure to a complexant should not further diminish but remain constant at the value measured in experiment (i). This is verified by experiment (iii), which in case of reversible inhibition only, should show the same activity in the presence of a complexing agent as was found in experiment (i). The latter was observed for compounds **1–3** shown in Table 3.These three compounds only show reversible inhibition and do not permanently inactivate the enzyme. This implies that the enzyme can be reused for next batches when exposed to either of these three compounds. This is an important observation as the enzyme accounts for a substantial part of the total cost of enzymatically prepared cephalosporins. It should be noted that compounds **1** and **3** are also effective in the complexation with Cephalexin and accordingly also suitable for the clathration mediated enzymatic synthesis of this antibiotic. In Table 3 the residual activity of Assemblase when exposed to either of the three complexing agents as a percentage of the enzyme activity in the absence of complexing agent is listed. These residual activities are similar to those measured after exposure to β-naphthol, a naphthalene derivative that has a significant beneficial effect on the yield of the enzymatic synthesis of Cephalexin.[12] Although a lower enzyme activity on itself is not desirable, it has the advantageous effect that it diminishes the diffusion limitations of Assemblase. This effect was observed for the enzymatic synthesis of Cephalexin using *in situ* clathration with β-naphthol and has been described in a quantitative manner using models developed for Assemblase and free Penicillin G acylase.[12]



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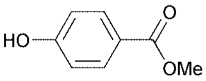

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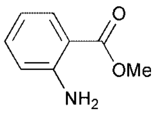

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Table 3 The residual activity of Assemblase in the presence of the complexants

Complexing agent	Residual activity (%)
2-Hydroxybiphenyl **1**	30
Methyl 4-hydroxybenzoate[17] **2**	30
Methyl 2-aminobenzoate **3**	40

Concluding remarks

From a series of benzene-derived complexants, three are effective in the clathration-mediated synthesis of Cephradine, *viz* methyl 2-aminobenzoate, 2-hydroxybiphenyl, and methyl 4-hydroxybenzoate.[17] These agents showed a reversible inhibitive effect on Assemblase resulting in a residual activity of approximately 30% when exposed to these compounds. Methyl 2-aminobenzoate and 2-hydroxybiphenyl are also effective in the clathration of Cephalexin. It is highly relevant to note that these three compounds have a low toxicity, and that two thereof are commonly used as preservatives of food products. Application of these toxicologically and environmentally acceptable complexing agents in the clathration mediated synthesis of Cephradine or other cephalosporin antibiotics has interesting prospects, which deserve further elaboration.

Experimental

For the analysis of the complexation experiments a Pharmacia LKB.LCC 2252 HPLC was used, with a reversed phase column (Merck 50983 LiChrospher 100RP18, 5 μm, 250 × 4 mm) and a UV detector ($\lambda = 254$ nm) of Farmacia LKB.UV-MII. An appropriate eluent for the analysis was a mixture of acetonitrile (HPLC grade) and a 50 mM phosphoric acid buffer with pH = 2.7. The pH stat apparatus used was a Schot Geräte Titrator TR154. Cephradine was a generous gift from DSM Research, Geleen, The Netherlands.

Efficiency measurements

Cephradine (524 mg) was dissolved in water (50 ml). The pH was adjusted to 7.2 and the solution was cooled to 5 °C. Complexing agent (1.5 mmol) was added as such to the stirred solution. The pH was maintained constant during the experiment by adding 5% HCl using a pH stat apparatus. After 90 min a sample was taken in duplo. The samples were filtered in order to remove the precipitated complex and subsequently analysed by HPLC. The residual Cephradine concentration was determined using standard solutions.

The compounds that have been tested in efficiency measurements are collected in Table 3. In the case of 2-phenylphenol, 4-methylacetophenone and methyl 4-hydroxybenzoate, 2 equivalents of complexant (3 mmol) were added as these compounds form 1 : 1 complexes with Cephradine, whereas the other compounds form 2 : 1 complexes.

Assemblase inhibition experiments[16]

The rate of phenylglycine amide hydrolysis is taken as a measure for the activity of Assemblase. Each experiment was performed under the following conditions:
0.2% (w/w) of Assemblase relative to phenylglycine amide, starting concentration of phenylglycine amide 80 mM, pH = 8, and $T = 20$ °C.

The activity measured during a blank experiment (in the absence of complexant) was taken as a reference, which was set as 100% activity. The residual activity of Assemblase in the presence of a complexing agent was expressed as a percentage of the activity measured during the blank experiment. The rate of the phenylglycine amide hydrolysis was followed by titration with 80 mM hydrochloric acid.

For the inhibition studies the complexant was added in an amount equimolar to phenylglycine amide. For each complexant three activity measurements where performed. First the activity of fresh Assemblase was determined in the presence of the complexing agent. In a second experiment fresh Assemblase was incubated for 16.5 h in the presence of the complexing agent. Next, the Assemblase was thoroughly washed with water and its activity was measured in the absence of complexing agent. For the third experiment fresh Assemblase was incubated during 16.5 h in the presence of complexing agent. After washing with water the activity of the biocatalyst was measured in the presence of the complexing agent.

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TiO_2/SO_4^{2-}: an efficient and convenient catalyst for preparation of aromatic oximes

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TiO_2/SO_4^{2-} solid superacid is an efficient reusable heterogeneous catalyst for the synthesis of aromatic oximes. Both aromatic aldehydes and ketones gave satisfactory results under mild and solvent free conditions. It is friendly to the environment.

Introduction

The conversion of aldehydes and ketones to oximes is an important chemical transformation, as the latter are readily prepared and highly stable compounds.[1] Oximes are useful protecting,[2] selective α-activating groups,[3] and they are extensively used for the purification and characterization of carbonyl compounds as well as in the preparation of amides.[4] They can also serve as intermediates of nitriles.[5]

Both acids and general bases can act as catalysts for the preparation of oximes. A number of catalysts have been documented, such as formic acid,[6] pyridine/chloroform,[7] ethanol/pyridine[8] and sulfuric acids.[9] They all have their own merits and shortcomings. Some methods are not very satisfactory due to drawbacks such as low yields, long reaction time and effluent pollution. Recently, a new process was developed for cyclohexanone oxime production by liquid-phase ammoximation of cyclohexanone using ammonia hydrogen peroxide as the oxidizing agent and titanium silicalite as the catalyst.[10] It is effective for several oximes,[11–16] but not economical owing to use of H_2O_2. CaO has been used as the catalyst for the formation of oximes;[17] the yields are high but the workup is tedious.

The challenge in chemistry to develop practical processes, reaction media, conditions and/or utility of materials based on the idea of green chemistry is one of the most important issues in the scientific community.[18] Recently, TiO_2/SO_4^{2-} solid superacid has been used as a catalyst for a variety of organic reactions.[19–22] Owing to our interest in solid-state reactions, we attempted to use TiO_2/SO_4^{2-} solid superacid as a catalyst for the preparation of aromatic oximes. Herein we report an efficient procedure for synthesis of aromatic oximes by reaction of aromatic aldehydes and ketones with hydroxylamine hydrochloride catalyzed by TiO_2/SO_4^{2-} solid superacid.

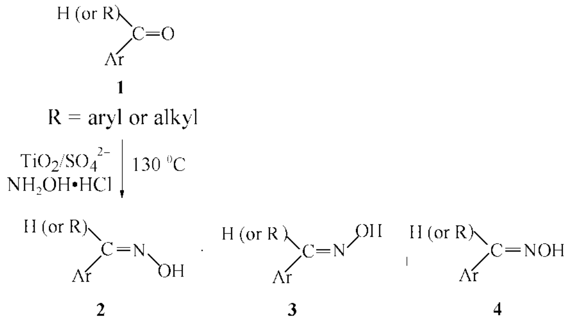
Results and discussion

Treatment of aromatic aldehydes (ketones) with hydroxylamine hydrochloride along with a catalytic amount of TiO_2/SO_4^{2-} solid superacid at 130 °C afforded aromatic oximes in excellent yields (Scheme 1). Various aldehydes (ketones) were used for this reaction. Some aldehydes yielded two isomers and high yields of oximes within 1 min (Table 1, entries 1, 2, 3, 5, 6, 7, 10, 11, 12), others gave only one isomer and lower yields (Table 1, entries 4, 8, 9, 13). Aromatic ketones were not as active as aromatic aldehydes owing to their higher steric hindrance; a longer time was required and lower yields were obtained. Anthrone (Table 1, entry 20) did not react at all within 2 h.

TiO_2/SO_4^{2-} solid superacid is superior to halogenous solid superacids and other liquid acids in terms of green chemistry. It has many advantages such as efficiency, non-pollutive and non-corrosive aspect and high activity in the temperature range of 773–873 K. TiO_2 soaked with $(NH_4)_2SO_4$ has a higher specific surface area than titanium dioxide, aluminosilicates or zeolites, as well as superior acidity. TiO_2/SO_4^{2-} solid superacid has thus been widely studied in hydrocracking of paraffins, dehydration of alcohols, esterification, alkylation of olefins, photochemical catalysis and protection of aldehydes, ketones and alcohols.

TiO_2/SO_4^{2-} solid superacid was prepared as follows: $Ti(OH)_4$ was treated with 1 mol L^{-1} $(NH_4)_2SO_4$ solution for 4 h, then dried in an oven at 110 °C for 2 h, calcined in a furnace at 500 °C for 4 h. Acid centers are formed which results in an acid strength (H_{0^-}) of 14.57 (Fig. 1).

From Fig. 1 we found that the acidity of Lewis acid centres on the surface of Ti^+ is enhanced owing to the strong inductive



Scheme 1

Green Context

Oximes are widely used in organic synthesis, in protection, in activation, and in purification and characterisation. Many methods have been developed to prepare oximes but they commonly suffer from some combination of low product yields, long reaction times and an unacceptable level of by-products. This paper describes a new greener method for synthesis of aromatic oximes from aromatic aldehydes and ketones. The method is based on the solid state reaction of the carbonyl compound and hydroxylamine in the presence of a solid acid. The procedure avoids solvent, gives high product yields for a range of substrates, and gives only water and HCl as by-products. ***JHC***

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Table 1 Synthesis of aromatic oximes from aromatic aldehydes and ketones catalyzed by TiO_2/SO_4^{2-}

Entry	Substance	Time/min	Products/Yields(%)[a] (mp/°C: found, lit[b])	
1	Benzaldehyde **1a**	1	**2a**/85 (129–130, 130)	**3a**/15 (34–35, 35)
2	*m*-Chlorobenzaldehyde **1b**	1	**2b**/85 (117–118, 118)	**3b**/15 (70–71, 70–71)
3	*p*-Chlorobenzaldehyde **1c**	1	**2c**/85 (145–146, 146)	**3c**/15 (110–111, 110)
4	2,4-Dichlorobenzaldehyde **1d**	1	**4d**/95 (136–137, 136–137)	
5	*m*-Nitrobenzaldehyde **1e**	1	**2e**/85 (84–85, 85)	**3e**/15 (122–123, 121–123)
6	*p*-Nitrobenzaldehyde **1f**	1	**2f**/85 (132–133, 133)	**3f**/15 (181–184, 182–184)
7	*p*-Methylbenzaldehyde **1g**	1	**2g**/85 (107–109, 108–110)	**3g**/15 (79–81, 79–80)
8	*o*-Hydroxybenzaldehyde **1h**	1	**4h**/96 (56–58, 57)	
9	*p*-Hydroxybenzaldehyde **1i**	1	**2i**/95 (114–116, 115–116)	
10	*p*-Methoxybenzaldehyde **1j**	1	**2j**/85 (132–134, 133)	**3j**/15 (44–46, 45)
11	Piperonal **1k**	1	**2k**/85 (111–112, 112)	**3k**/15 (145–146, 146)
12	*p*-Dimethylaminobenzaldehyde **l**	1	**2l**/85 (184–185, 185)	**3l**/15 (143–144, 144)
13	Vanillin **1m**	1	**4m**/96 (120–122, 121–122)	
14	*m*-Nitroacetophenone **1n**	2	**4n**/95 (130–132, 131–132)	
15	*p*-Nitroacetophenone **1o**	2	**4o**/95 (173–174, 174)	
16	*p*-Aminoacetophenone **1p**	2	**4p**/95 (147–148, 147–148)	
17	*p*-Chloroacetophenone **1q**	2	**4q**/95 (94–95, 95)	
18	Dibenzyl ketone **1r**	10	**4r**/90 (124–125, 125)	
19	Benzophenone **1s**	120	**4s**/75 (142–144, 143–144)	
20	Anthrone **1t**	120	No reaction	

[a] Yields refer to isolated products. [b] Lit. data from *Dictionary of Organic Compounds*, 6th edn.

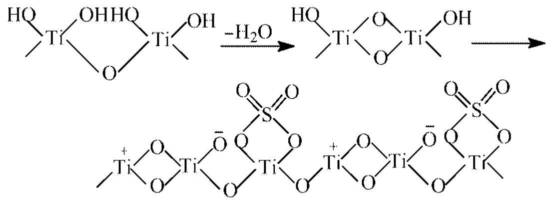

Fig. 1 Formation of TiO_2/SO_4^{2-}.

effect of S=O. When the catalyst absorbs some water, H^+ is readily ionized to form Brönsted acid centers. These two kinds of acid center can readily interconvert, which is favorable for the acidity of TiO_2/SO_4^{2-}.

The TiO_2/SO_4^{2-} solid superacid catalyst was filtered after the reaction, washed with ethyl acetoacetate and then dried at 110 °C for 1 h. The synthesis of oxime (**4o**) was respected five times without any significant decrease in activity. Further recycling led to loss of efficiency of the catalyst owing to absorption of organics. Organics on the solid surface result in reduction of the number of active centers. Also SO_4^{2-} on the catalyst was lost during washing. Organic species could be removed at high temperature reactivating the catalyst.

In conclusion, the formation of oximes is achieved effectively using TiO_2/SO_4^{2-} solid superacid under mild and solvent free conditions. The operation is simple, the reaction time is short and the yields are high in an environmentally friendly process.

Experimental

Liquid aldehydes were purified by distillation prior to use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^1H NMR spectra were measured on a Bruker AC-80 (80 MHz), spectrometer using TMS as internal standard and $CDCl_3$ as solvent. MS were determined on a VG-7070E spectrometer (EI, 70 eV). Melting points were uncorrected. The products were identified by IR, MS, ^1H NMR spectra and by comparison of their melting points with literature values.

A mixture of aromatic aldehyde or ketone (2 mmol), hydroxylamine hydrochloride (3 mmol) and powdered of TiO_2/SO_4^{2-} solid superacid (50 mg) was ground in a mortar, then added to a 25 ml flask. The mixture was stirred with a magnetic stirrer for the time indicated in Table 1, and HCl generated in the reaction was absorbed by CaO and NaOH in a drying tube. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, mixed with ethyl acetate, and the catalyst filtered off. Ethyl acetate was then removed *via* a rotary evaporator under reduced pressure to give the products. The products were purified and isomers were separated by column chromatography on silica gel using petroleum and diethyl ether as eluant.

Acknowledgment

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Microwave activation and solvent-free phase transfer catalysis for the synthesis of new benzylidene cineole derivatives as potential UV sunscreens

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Microwave activation coupled with solvent-free phase transfer catalysis (PTC), as a green chemistry procedure, was applied to the synthesis of new benzylidene cineole derivatives as potential UVA filters. Considerable improvements over classical procedures are put into evidence when using KOH + K_2CO_3 as the base and TBAB as the phase transfer agent. Comparison with conventional heating in strictly the same conditions as under microwave revealed an important specific non-thermal microwave effect. Preliminary studies to evaluate the photochemical behaviour of these new derivatives were carried out.

Introduction

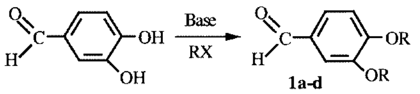
It is now well known that, in organic synthesis, solvent-free conditions are especially adapted to microwave activation and lead to increased safety and environmental respect.[1] The aim of this work was to apply these methodologies, as eco-friendly and economical procedures for a 'Green Chemistry',[2] to the synthesis of new benzylidene cineole derivatives, interesting as potential UV sunscreens. In a previous work,[3] a series of 5-[4-alkoxybenzylidene]-1,3,3-trimethyl-2-oxabicyclo[2.2.2]-octan-6-ones, related to the 3-benzylidenecamphor derivatives (a well known class of UV filters) were synthesized under classical conditions and evaluated for potential cosmetic applications as UV sunscreens. Since an ideal sunscreen should show a high extent of substantivity without penetrating the skin, these compounds were evaluated as regards their *in vitro* percutaneous absorption. Some of them showed a little skin permeation, especially those with a long alkoxylic chain.

In pursuing our research in this field, we have synthesized a new series of cineole derivatives, 5-[3,4-bis(alkoxy)benzylidene]-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-ones **2a–d** in order to obtain new compounds with a greater rate of substantivity. Previously the reactions were carried out under classical conditions (organic solvent, thermostated oil-bath) and suffered of some difficulties: long reaction times (24 h), large solvent amounts, work-up complexity. Our increasing interest in efficient, economical and clean technologies has promoted the research in the field of microwave irradiation under dry conditions, using solid–liquid solvent-free phase transfer catalysis (PTC), a specific efficient method for anionic reactions.[4,5] In order to check the possible intervention of non-thermal microwave effects, the best experiments in 'dry media' were carried out in a thermostated oil-bath, under the same conditions as under microwaves (time, temperature, vessel), with an accurate control of the profile in raising of temperature in both conditions.

Preliminary studies to evaluate the photochemical behaviour of these new benzylidene derivatives, given these products are potential UV sunscreens, were carried out on compound **2a** by investigating the photoinduced *cis–trans* isomerization by UVA–UVB radiation.[6,7]

Results and discussion

The syntheses of compounds **2a–d** were performed in a two-step procedure: synthesis of 3,4-dialkoxybenzaldehydes **1a–d** (Scheme 1, Table 1) by alkylation of 3,4-dihydroxybenzaldehydes[8,9] and subsequent condensation (Knoevenagel reaction) of these products with 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-one (Scheme 2, Table 2).[10,11]



Scheme 1

Table 1 3,4-Dialkoxybenzaldehydes **1a–d**

Compound	R	Mol. wt.	Mp[a]/°C
1a	$C_{12}H_{25}$	475	73–75
1b	$C_{14}H_{29}$	531	76–77
1c	$C_{16}H_{33}$	586	81–82
1d	$C_{18}H_{37}$	643	83–85

[a] From 95% ethanol.

Green Context

Solvent free organic synthesis is an important part of green chemistry. Avoiding a solvent reduces the number of components in a reaction, stops any solvent emission problems, and gets around any solvent recycling requirements. This paper describes the combination of microwave activation and solvent-free phase transfer catalysis to achieve a new green chemistry procedure for the synthesis of new benzylidene cineole derivatives. Preliminary studies on the photochemical behaviour of these compounds has also been carried out with the possibility of their use as UV sunscreens in mind. ***JHC***

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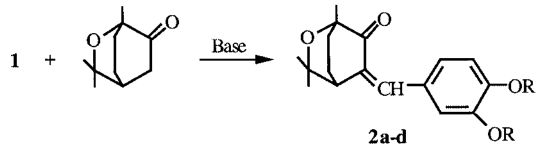

Scheme 2

Table 2 5-[3,4-bis(alkoxy)benzylidene]-1,3,3-trimethyl-2-oxabicyclo-[2.2.2]octan-6-ones **2a–d**

Compound	R	Mol. wt.	Mp[a]/°C	λ_{max}/nm (log ε)[b]
2a	$C_{12}H_{25}$	625	36–38	326 (4,21)
2b	$C_{14}H_{29}$	681	44–45	325 (4,21)
2c	$C_{16}H_{33}$	737	53–54	326 (4,22)
2d	$C_{18}H_{37}$	793	59–60	325 (4,23)

[a] From propan-2-ol. [b] In cyclohexane.

The classical and the solvent-free methods for the synthesis of these compounds are reported. To optimize the reaction conditions, several experiments were carried out to synthesize the dialkoxybenzaldehyde **1a** and the corresponding benzylidene derivative **2a** using tetra-*n*-butylammonium bromide (TBAB) and methyltri-*n*-octylammonium chloride (Aliquat 336) as catalysts. The most efficient methods were selected to synthesize the parent compounds.

3,4-dialkoxybenzaldehydes 1a–d

Several methods were selected:

1: Classical method, K_2CO_3 in acetone using a thermostated oil bath
2: Microwave activation, K_2CO_3+KOH/TBAB
3: Microwave activation, KOH/Aliquat
4: Microwave activation, K_2CO_3+KOH/Aliquat
5: Microwave activation, KOH/TBAB
6: Microwave activation, K_2CO_3/TBAB
7: Thermostated oil bath heating, K_2CO_3+KOH/TBAB

The reaction conditions and the results related to the synthesis of **1a–d** are given in Table 3.

The best results are obtained under microwave activation coupled with solid–liquid solvent free phase transfer catalysis (PTC) using a mixture of KOH+K_2CO_3 (1:1) as the base and TBAB as the catalyst (method 2). This method leads to higher yields within a much shorter reaction time when compared to the classical method (method 1). Other bases/catalysts systems lead to lower yields.

For compounds **1a** and **1d** we have compared conventional heating (method 7) and microwave activation (method 2), using K_2CO_3+KOH/TBAB, under otherwise similar conditions. The results evidence a very strong specific microwave effect (yields MW/: 86/18% for compound **1a**; 80/10% for compound **1d**). Such a conclusion is strengthened by the examination of the identical rise in temperature for both types of activation studied for compound **1a** (Fig. 1). Under conventional heating, the reaction time for this compound was extended up to 5 h and the yield was only 46% despite the total conversion.

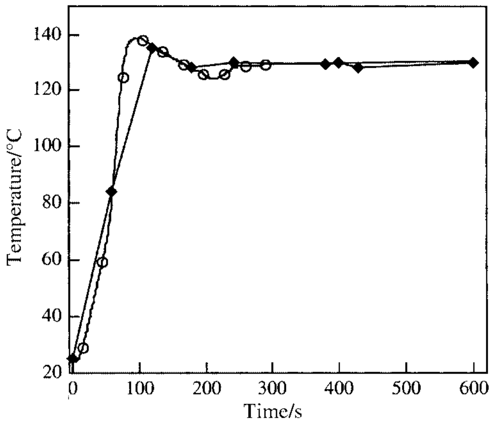

Fig. 1 Profiles of raise in temperature by microwave irradiation (○) (method 2) and classical heating (◆) (method 7) for the synthesis of compound **1a**.

5-[3,4-bis(alkoxy)benzylidene]-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-ones 2a–d

Several methods were checked:

1: Classical method, MeONa in THF using thermostated oil bath
2–7: The same microwave methods as above were employed.

Table 3 3,4-Dialkoxybenzaldehydes **1a–d**: reaction conditions and yields

Compound	Method		Time/min	Temp[a]/°C	Yield (%)
1a	1 Classical (K_2CO_3/acetone)	△	1440	Reflux	66[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**10**	**130**	**86**[b]
	3 KOH/Aliquat	MW	10	130	65[b]
	4 K_2CO_3 + KOH/Aliquat	MW	10	130	68[b]
	5 KOH/TBAB	MW	10	130	14[c]
	6 K_2CO_3/TBAB	MW	10	130	0[c]
	7 K_2CO_3 + KOH/TBAB	△	10	130	18[c,d]
		△	300	130	46[b,d]
1b	1 Classical (K_2CO_3/acetone)	△	1440	Reflux	58[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**10**	**130**	**80**[b]
	3 KOH/Aliquat	MW	10	130	56[b]
1c	1 Classical (K_2CO_3/acetone)	△	1440	Reflux	49[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**10**	**130**	**81**[b]
	3 KOH/Aliquat	MW	10	130	74[b]
1d	1 Classical (K_2CO_3/acetone)	△	1440	Reflux	62[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**10**	**130**	**80**[b]
	3 KOH/Aliquat	MW	10	130	70[b]
	7 K_2CO_3 + KOH/TBAB	△	10	130	10[c,d]

MW = Microwave activation, temperature monitored by power modulation (15–300 W); △ = Classical heating.
[a] Final temperature evaluated by IR detection for MW and by digital thermometer for △ methods. [b] Yields refer to pure isolated products. [c] Yields obtained by RP-HPLC. [d] Complement: starting material.

Table 4 5-[3,4-bis(alkoxy)benzylidene]-1,2,2-trimethyl-2-oxabicyclo[2.2.2]octan-6-ones **2a–d**: reaction conditions and yields

Compound	Method		Time/min	Temp[a]/°C	Yield (%)
2a	1 Classical (MeONa/THF)	△	1440	Reflux	51[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**60**	**140**	**80**[b]
	3 KOH/Aliquat	MW	60	140	33[b]
	4 K_2CO_3 + KOH/Aliquat	MW	60	140	12[b]
	5 KOH/TBAB	MW	60	140	0[c]
	6 K_2CO_3/TBAB	MW	60	140	0[c]
	7 K_2CO_3 + KOH/TBAB	△	60	140	13[c,d]
		△	720	140	17[c,d]
2b	1 Classical (MeONa/THF)	△	1440	Reflux	60[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**60**	**140**	**78**[b]
	3 KOH/Aliquat	MW	60	140	39[b]
2c	1 Classical (MeONa/THF)	△	1440	Reflux	65[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**60**	**140**	**81**[b]
	3 KOH/Aliquat	MW	60	140	37[b]
2d	1 Classical (MeONa/THF)	△	1440	Reflux	68[b]
	2 K_2CO_3 + KOH/TBAB	**MW**	**60**	**140**	**87**[b]
	3 KOH/Aliquat	MW	60	140	30[b]
	7 K_2CO_3 + KOH/TBAB	△	60	140	19[c,d]

MW = Microwave activation, temperature monitored by power modulation (15–300 W); △ = Classical heating.
[a] Final temperature evaluated by IR detection for MW and by digital thermometer for △ methods. [b] Yields refer to pure isolated products. [c] Yields obtained by RP-HPLC. [d] Complement: starting material.

The reaction conditions and the results relating to the synthesis of these new benzylidene derivatives (**2a–d**) are reported in Table 4.

It appears clearly that microwave activation coupled with solid–liquid solvent-free PTC (KOH+K_2CO_3/TBAB) (method 2) is the most efficient 'dry system'. Good yields (78–87%) are obtained within shorter reaction times when compared to the classical procedure (method 1) (yields: 51–68%). Comparaison with conventional heating (method 7) in a thermostated oil-bath under the same conditions (time, temperature, vessel) shows again a very strong specific microwave effect (yields MW/Δ: 80/13% for **2a**; 87/19% for **2d**) supported by an accurate examination of the identical temperature rise profiles, studied for compound **2a** (Fig. 2). Under conventional heating, the reaction time for this compound was extended up to 12 h and the yield was only 17% despite total conversion.

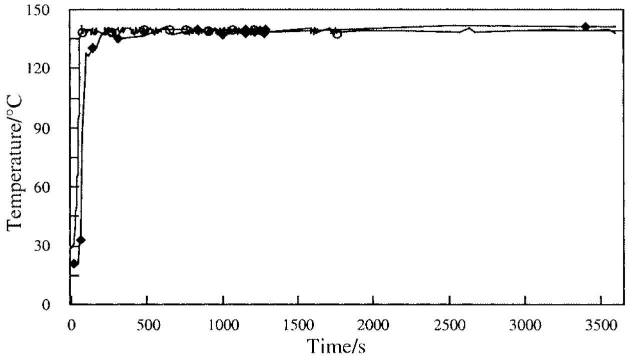

Fig. 2 Profiles of raise in temperature by microwave irradiation (○) (method 2) and classical heating (◆) (method 7) for the synthesis of compound **2a**.

In both types of studied reactions, phenoxide alkylation (Scheme 1) and aldolic condensation (Scheme 2), the specific non-thermal microwave effects, evidenced by strict comparison of MW and Δ activation, can be attributed to the evolution of the polarity of the system during the progress of the reaction. This is provided by ionic dissociation (*i.e.* polarity increase) of the ion pairs from the ground state of the reaction towards the transition state,[12] which is more polar due to the negative charge delocalization (see for instance Scheme 3 for the alkylation step):

$$ArO^-,M^+ + R\text{–}X \rightleftharpoons [\,^{\delta-}ArO\text{---}R\text{---}X^{\delta-},\ M^+\,]^{\neq}$$

Scheme 3

Condensation of the cineole ketone **1** with the appropriate dialkoxybenzaldehyde leads exclusively to the *trans* isomer which is thermodynamically more stable. The *trans* structure is attributed by ^1H NMR spectral data considering the chemical shift of the vinylic proton. As an example, the ^1H NMR spectrum of compound **2a** in the *trans* form is shown (Fig. 3).

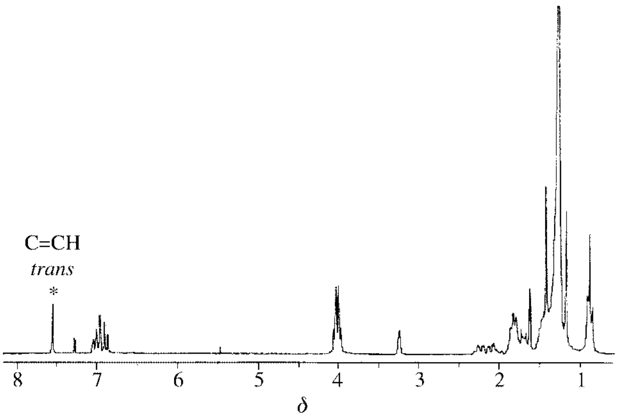

Fig. 3 ^1H NMR spectrum of compound **2a**.

The photochemical behaviour of the new compounds was investigated by irradiating, for instance, compound **2a** with UV light produced by two UVA or UVB lamps (0.3–36 J cm^{-2}). With regard to the UVB radiation, an increasing photoinduced *cis–trans* isomerization of compound **2a** was observed (Fig. 4).

The *cis–trans* percentage ratio was detected by RP-HPLC. A 12% *cis* conversion was observed after an irradiation dose of 0.3 J cm^{-2}. This conversion increased until a photostationary equilibrium was reached at 18 J cm^{-2} (*trans*/*cis*: 45/55) (Fig. 5). No degradation products were observed for the entire range of irradiation doses.

UVA radiation leads to a slower isomerization which can be detected only at 32 J cm^{-2} (*cis* conversion: 5%). No degradation products were observed for the entire range of irradiation doses.

The isomerization was monitored by TLC and by RP-HPLC.

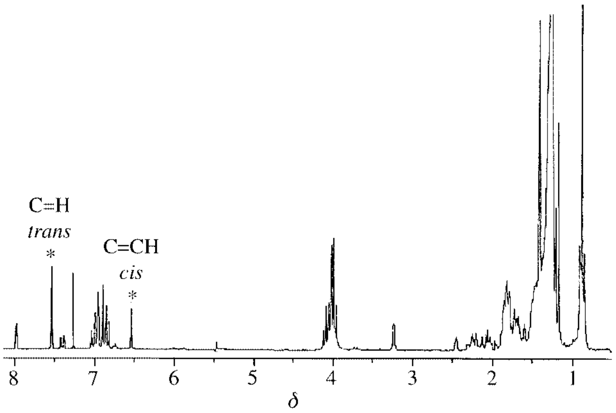

Fig. 4 ^{1}H NMR spectrum of compound **2a** after UVB irradiation (4.5 J cm^{-2}).

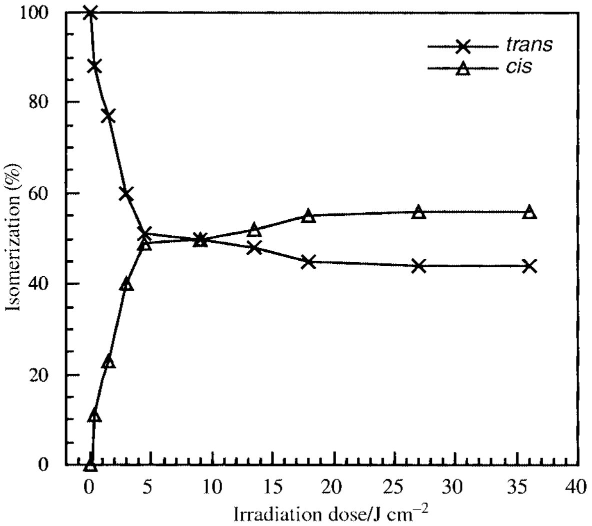

Fig. 5 Photoisomerization of compound **2a**: amount (%) of *trans* and *cis* forms as a function of UVB irradiation dose.

Experimental

General

The equipment for microwave irradiation was a monomode reactor (Synthewave™402-Prolabo) specially designed for organic syntheses with an accurate control of temperature by IR detection.[13]

IR spectra were registered with a Perkin-Elmer 398 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian-Gemini 200 instrument (200 MHz) with TMS as internal standard; chemical shifts are reported as δ (ppm) relative to TMS. UV spectra were recorded on a Perkin-Elmer Lambda 3 spectrophotometer. UVB radiation was performed with a parallel bank of two UVB Philips TL20W/12R fluorescence tubes (Sara s.r.l., Castellanza, Varese, Italy) emitting a continuous spectrum between 280 and 320 nm with a peak emission at 312 nm.

UVA radiation was performed with a parallel bank of two UVA Philips TL40W/10R fluorescence tubes (Sara s.r.l., Castellanza, Varese, Italy) emitting a continuous spectrum between 320 and 390 nm with a peak emission at 365 nm. Irradiance measurements were carried out using a UVX digital radiometer (UVP inc., San Gabriel CA-USA).

Analytical HPLC procedures were performed with a Hewlett–Packard 1100 liquid chromatograph equipped with a Merck LichroCart 250-4 Purospher RP18 (5 μm) column and a DAD detector.

Elemental analyses for C and H were performed on a CE Instruments - EA 1110 CHNS-O analyser. Melting points were determined on a Büchi 510 apparatus and were uncorrected. Oil bath temperature measurements were carried out using a digital thermometer Comark C9007.

The IR and ^{1}H NMR spectra of all synthesized compounds were in agreement with the proposed structures. Microanalysis for C and H were within ± 0.3% of the theoretical values.

Classical synthesis of compounds 1a–d

A solution of 3,4-dihydroxybenzaldehyde (2.76 g, 20 mmol) and an appropriate alkyl halide (40 mmol) in anhydrous acetone (50 mL) were added to a suspension of anhydrous K_2CO_3 in anhydrous acetone (100 mL) and refluxed for 24 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was extracted thoroughly with dichloromethane (100 mL). The extracts were dried on $MgSO_4$, filtered and evaporated under reduced pressure. The crude product obtained was purified by recrystallization from 95% ethanol.

Classical synthesis of compounds 2a–d

1.68 g (10 mmol) of (+)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-one and the corresponding dialkoxybenzaldehyde (10 mmol) were added to a suspension of sodium methoxide (10 mmol) in THF, prepared from sodium (0.23 g) and anhydrous methanol (20 mL). The reaction mixture was refluxed for 24 h. After cooling to room temperature, THF was removed under reduced pressure; the residue was treated with water and extracted thoroughly with dichloromethane. The extracts were dried on $MgSO_4$, filtered and evaporated under reduced pressure and the crude product obtained was purified by recrystallization from propan-2-ol.

Microwave mediated synthesis of compounds 1a–d

In a 40 mL Pyrex tube, 1.38 g (10 mmol) of 3,4-dihydroxybenzaldehyde were mixed together with 1.12 g (20 mmol) of powdered KOH, 2.8 g (20 mmol) of anhydrous K_2CO_3, 0.32 g (1 mmol) of TBAB and 22 mmol of the appropriate alkyl halide. The reaction mixture was introduced into the microwave reactor and irradiated for 10 min at 130 °C under stirring (maintaining the temperature by power modulation from 15 to 300 W). After cooling to room temperature, the organic product was recovered by elution with dichloromethane (50 mL) and subsequent filtration on Florisil with a Gooch filter, to remove the mineral salts and catalyst. The solution was evaporated under reduced pressure and the crude product was purified by recrystallization from 95% ethanol.

Microwave mediated synthesis of compounds 2a–d

In a 40 mL Pyrex tube, 1.68 g (10 mmol) of (+)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-one were mixed together with 1.12 g (20 mmol) of powdered KOH, 2.8 g (20 mmol) of anhydrous K_2CO_3, 0.32 g (1 mmol) of TBAB and the corresponding dialkoxybenzaldehyde (10 mmol). The reaction mixture was introduced into the microwave reactor and irradiated under stirring for 60 min at 140 °C, maintaining this temperature by power modulation from 15 to 300 W. After cooling to room temperature, the organic product was recovered by elution with dichloromethane (50 mL) and subsequent filtration on Florisil. The solution was evaporated under reduced pressure and the crude product was purified by recrystallization from propan-2-ol.

As an example, IR and ^{1}H NMR spectral data of the *trans* isomer of compound **2a** are reported: IR ($CHCl_3$) ν/cm^{-1}: 1710 C=O, 1600 C=C; δ_H ($CDCl_3$): 0.88 (t, *J* 4.8 Hz, 6H, $2CH_3$); 1.17 (s, 3H, CH_3); 1.26 (near s, 31H, $14CH_2$, CH_3); 1.42 (s, 3H, CH_3); 1.55–1.85 (m, 12H, $6CH_2$); 1.95–2.40 (m, 4H, $2CH_2$); 3.24 (br s, 1H, H-4); 4.0 (q, *J* 6.0 Hz, 4H, $2CH_2O$); 6.85–7.05 (m, 3H, C_6H_3); 7.54 (s, 1H, C=CH *trans*).

Comparative conventional heating for synthesis of compounds 1a, 2d, 2a and 2d

For the sake of comparison and to check possible non-thermal microwave effects, the best results obtained under microwaves were extrapolated to conventional heating. We thus used a thermostated oil-bath under exactly the same conditions (time, temperature, pressure, medium and reaction vessel, stirring system and reaction speed) including similar profiles of raising in temperature: 10 min at 130 °C for **1a** (Fig. 1) and **1d**, 60 min at 140 °C for **2a** (Fig. 2) and **2d**.

Photochemical behaviour

Compound **2a** was investigated in cyclohexane by irradiating the solution for different amounts of time with increasing UVA and UVB light doses, in a range from 0.3 to 32 J cm^{-2} (mW cm^{-2} $\times$ sec = mJ cm^{-2}). The system was aerated to avoid thermal influence. Samples were placed 25 cm from UVA and UVB lamps the intensities of which were 4.0 and 2.5 mW cm^{-2}, respectively.

The isomerization was monitored by TLC [chloroform–cyclohexane (65:35)] on precoated aluminium sheet silica gel 60F$_{254}$ and the samples were then processed by RP-HPLC using a mobile phase of acetonitrile/tetrahydrofurane (75:25) (flow 0.5 ml min^{-1}) to quantify the percentage of the two isomers.

Conclusion

The synthesis of new benzylidene cineole derivatives and of their precursor aldehydes, carried out by classical methods, require very long reaction times and difficult work-up procedures. The use of microwave irradiation coupled with solid–liquid solvent-free phase transfer catalysis (TBAB) leads to a considerable increase of yields, significant reduction in the reaction times and simplification in work-up.

These results are very interesting in the cosmetic field where the purity of ingredients, increased safety and cost reduction are very important features.

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