Green Chemistry

Editorial

In the last issue of *Green Chemistry* I highlighted the growing importance of renewable resources as feedstocks for the chemical industry in the 21st century. The area is not only vital to the long-term survival of chemical manufacturing, but also provides new and stimulating challenges for chemical research. Renewable resources will impinge on many future issues in environmental chemistry and we can also expect the same of chemical and process engineering including novel techniques. The successful development of many new and exciting research areas in green chemistry will require a substantial input from engineers. This is especially true when fundamentally new chemical reaction systems and methods are involved. The application of unusual solvent systems such as those based on highly volatile supercritical fluids or extremely involatile ionic liquids to the synthesis of fine chemicals, for example, will require unconventional reactor systems. Even the translation of technologies from one sector to another will necessitate a reconsideration of traditional plant. Thus while the petrochemical sector now regards the use of solid catalysts as the norm, manufacturers of fine and speciality chemicals are more familiar with homogeneous systems. The use of a simple stirred vessel for mixing reactants and a solid catalyst may often be a greener alternative to existing processes but it presents significant difficulties at the separation stage and alternative reactor designs need to be considered.

We should not assume that the role of chemical and process engineers is always to respond to a challenge, which results from new chemistry. Engineers can also take the lead as is witnessed for example in the drive towards intensive processing. Here a completely different way of thinking about chemical manufacturing is leading to the design of imaginative new reactors and the chemists now need to develop suitable new chemistry to complete the clean process equation. Collaboration between engineers and chemists is also necessary to help progress some of the alternative techniques that are now quite routinely being applied to help clean up chemical syntheses. Microwave heating of organic reaction systems, for example, can offer savings in reaction time and energy consumption, as well as improvements in selectivity through quicker and more focussed heating. In this issue of *Green Chemistry* we can read about another useful technique in the armoury of the green chemist, sonochemistry. This non-hazardous radiation can be applied to a very wide range of reactions and its use can lead to significant improvements in reaction selectivity and product yield. There are many challenges ahead for green chemistry and it is very important that the chemists and the engineers work together towards their solutions. It is encouraging to see initiatives in the UK and elsewhere to promote Chemistry–Chemical Engineering partnerships. We must work hard to foster and encourage them. I hope to see an increasing number of articles from these partnerships in future issues of *Green Chemistry.*

Regular readers of *Green Chemistry* will be pleased to read that I do not intend to write every editorial! We are now working on a schedule, which will enable the journal to feature editorial articles from other members of the editorial board, and from ‘guests’ who are key players in the world of green chemistry. There is little doubt that green chemistry is now a global phenomenon. As I prepare for a trip to Japan following in the footsteps of Paul Anastas, Ken Seddon is heading for China. I am delighted to hear of the development of green chemistry in Australia and I was encouraged on a recent trip to Israel by the determination of the Ministry of the Environment to implement green chemistry practices in their chemical manufacturing. The first Italian awards for green chemistry have recently been announced and the European Vth framework for research with a strong emphasis on ‘green’ chemistry is now fully launched. We can also look forward to significant conferences and other meetings on aspects of green chemistry in France, China, Italy, the UK and the USA. Of course the USA is where green chemistry was born and so it seems particularly appropriate that our US Associate Editor will write the Editorial for the next issue of *Green Chemistry*.

James Clark, York, May 1999

Oilseed rape

As a source of diesel

Oilseed rape could supply 10% of the UK's diesel requirements by 2020 if the tax on its purchase was reduced to 10% of that on fossil-sourced diesel. Its use could be increased by blending it into fossil diesel, as is the practice in France and Sweden. Biodiesel is cleaner than fossil-diesel: its carbon dioxide emissions are balanced by its fixation in the plant and it requires no added sulfur lubricant (British Association for Bio Fuels and Oils Report) (*Crops*, 1999, **17**, 10).

As a provider of renewable industrial feedstocks

ACTIN, the Alternative Crops Technology Interaction Network, is running a seminar entitled ‘The Oilseed Rape Pipeline’ at the Manchester Conference Centre, UK, on June 8, 1999 to illustrate the potential of oilseed rape as a provider of renewable industrial feedstocks, now and in the future. The programme includes papers on:

- Oilseed rape–the crop, its origins and potentials
- Novel fatty acids from oilseed rape
- Rapeseed oil as a chemical feedstock
- The economic viability of the oilseed rape pipeline
- The needs of the oleochemical industry
- Composites and plastics from oilseed rape meal
- Rapeseed as a source of polyurethanes
- Sourcing erucic acid
- Vegetable oil-based lubricants and hydraulic fluids

Further information can be obtained from Louise Wilkinson on the ACTIN help desk [Tel +44 (0)1372 802054; Fax +44 (0)1372 802245; Email info@actin.co.uk; http://www.actin.co.uk/about_actin/actin 2020/2020d_osr.htm]

Methyl bromide lives on

Phaseout delay

Both the USA and the EC have decided not to implement their earlier decision to bring forward the phaseout for methyl bromide use from the original 2005 date scheduled by the Montreal Protocol (*Green Chemistry*, 1999, **1**, G5). This is a recognition of the fact that acceptable alternatives are difficult to find. It is also evident that despite its toxicity it has been used for 50 years with a very good safety record because of its carefully controlled use. A large reduction in its escape into the atmosphere through effective methods of capture after use could greatly reduce its threat to the environment. The EC has also stated that the exemptions for the fumigation of goods in quarantine for pre-shipment will not be removed. All signatories to the Montreal Protocol have already agreed to a 50% reduction in the use of methyl bromide in 2001 (*International Pest Control*, 1999, **41**, 4).

Search for alternatives

A great deal of effort, especially at the US Department of Agriculture Agricultural Research Service (USDA-ARS), is going into the search for methyl bromide alternatives. The following are some of the avenues being explored:

- cylinderized phosphine
- methyl iodide
- benzaldehyde
- chitinase
- genetic manipulation of nematode genes to obviate the need for any chemical alternatives

The use of plastic sheeting to cover crops before fumigation with methyl bromide is also being explored as a means of reducing the fumigant escaping into the atmosphere to minimum levels.

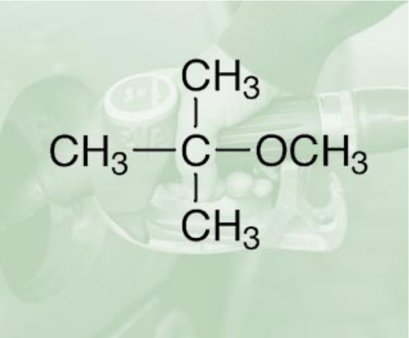
For further information on the methyl bromide phaseout and the search for alternatives see *Pesticide Outlook*, **9**(1), 4; **10**(2), 5 and the USDA ARS Methyl Bromide Website at http://www.ars.usda.gov/is/mb/mebrweb.htm.

Propyl bromide under threat too?

The EPA is considering adding *n*-propyl bromide (1-bromopropane) to its list of substances covered by the Significant New Alternatives Policy (SNAP) under the Clean Air Act which aims to phase out ozone-depleting substances and replace them with safer alternatives. *n*-Propyl bromide is used in aerosols, adhesives, coatings and solvents. The EPA may also set a limit in the range of 50-100 ppm for workplace exposure. Toxicity studies and further consideration of the damage to the environment are underway (*Chemical Market Reporter*, March 15, 1999).

MTBE phase-out in California

On 25 March 1999 California Governor Gray Davis issued an Executive Order ‘for the removal of methyl tertiary butyl ether (MTBE) from gasoline in California at the earliest possible date, but not later than 31 December 2002’. MTBE has been used since the late 1970s in relatively low concentrations to increase octane ratings in premium grade fuels, and since the early 1990s in much higher concentrations (up to 15%) to enhance gasoline combustion and reduce tailpipe emissions; MTBE has thus contributed to significant reductions in carbon monoxide and ozone levels. There has, however, been increasing concern about groundwater and surface water contamination with MTBE, which the US Environmental Protection Agency (EPA) has classified as a potential human carcinogen. The domestic fuel ethanol industry is prepared to step in immediately and provide a safe alternative while maintaining the clean air benefits of oxygenated gasoline use in the state. The most likely scenario would suggest refiners will replace MTBE with ethanol in northern California immediately and in southern California beginning in September 1999 when the VOC control season ends. This would eliminate the need for significant refinery modifications in the short term. In the longer term, refiners could phase in the use of ethanol in the summer months through refinery modifications allowing for the production of appropriate blendstocks. The California Department of Food and Agriculture has concluded that with existing supplies of rice straw, forest residue and other agricultural waste products, there is the potential for 2 bn gallons of ethanol production in California alone, about four times the amount of ethanol required to meet all of California's oxygenate demand in the absence of MTBE. A recent California Energy Commission concluded ethanol is the most cost effective alternative to MTBE, including non-oxygenated fuel, and will actually save money for California consumers in the long term.



$$CH_3-\overset{\displaystyle CH_3\atop|}{\underset{|\atop\displaystyle CH_3}{C}}-OCH_3$$

For more information see http://water.wr.usgs.gov/mtbe

All cars to be green?

The EU is considering legislation that would require the automotive industry to manufacture vehicles containing only 5% virgin material and at least 95% from recycled materials by 2015. Safer disposal would also be another requirement of the legislation and demands may also be placed on the quantities of toxic materials used during vehicle construction. In Europe, 8M cars per year are sent for scrap to give 9M tonnes of waste which is 75% recycled with the remainder mainly going to landfill or incineration (*European Chemical News*, 1999, **70**, 26).

Green pressure-sensitive tapes

Pressure-sensitive tapes are becoming increasingly popular due to their ease of use and lower end user costs when compared to other bonding systems. 100% solids radiation-cured adhesive systems are now taking over from solvent or waterborne coatings enabling fast line speeds and little or no solvent emissions. Such new technology will help the industry to meet stricter legislation such as the EPAs maximum achievable control technology standard that will require major modification to many of industry’s emission systems (*Adhesives Age*, 1999, **42**, 16).

Waste not want not

A new ammonium thiosulfate plant will use as its raw material sulfur- and ammonia-rich effluents from a refinery. Ammonium thiosulfate is used as a fertilizer. The plant will be built by Haldor Topsoe Engineering under contract to Statoil, near Copenhagen. The volume of these effluents is increasing due to ever-increasing requirements for desulfurised fuels. By using these effluents, the environmental damage caused by the SOx and NOx emissions resulting from their incineration will be avoided. The plant will use a new Topsoe process and will benefit from a Danish Government grant of DKr 12M.

Halons

While the emissions of most ozone-depleting chemicals have stabilised or been reduced since 1988, the levels of Halon-1211 are increasing, reports the CSIRO in Australia. Measurements of this halon, which is used as a fire retardant, over Tasmania show that it is increasing by 200 tonnes per year. The CSIRO are claiming that it is now responsible for 20% of worldwide ozone depletion. China produces 90% of the world's output of Halon-1211 and they, along with other developing countries, have until 2010 to phase out halons (*European Chemical News*, 1999, **70**, 24; *Chemische Rundschau*, 1999, **52**, 10).

On December 21, 1998, the European Council of Ministers agreed on a proposal of regulations on the use and production of ozone depleting chemicals (ODSs). The proposal would go beyond the requirements of the Montreal Protocol, including a ban on the sale and use of halons after December 31, 2002 (except for critical uses) with mandatory decommissioning a year later, and import/export restrictions. The proposal is expected to be voted on by the European Parliament sometime this summer.

Halon extinguisher

For more information on halon alternatives see the web sites of the Halon Alternatives Research Corporation (http://www.harc.org/) and the UNEP Halons Technical Options Committee (http://www.teap.org/html/halons.html) and links therein.

Persistant organic pollutants

In February 1997, the Governing Council of the United Nations Environment Programme (UNEP) adopted Decision 19/13C to promote measures to reduce and/or eliminate releases of persistent organic pollutants known to cause serious adverse effects to humans even at very low doses. The decision called on UNEP to convene an Intergovernmental Negotiating Committee (INC) to prepare an internationally binding instrument aimed at minimising POPs. The negotiations began with a meeting of representatives of over 100 governments in Montreal in June/July 1998. The Montreal talks (INC-1) focuses on twelve POPs: aldrin, chlordane, DDT, dieldrin, dioxins, endrin, furans, heptachlor, hexachlorobenzene, mirex, PCBs and toxaphene. Significant progress was made at the INC-2 meeting held in Nairobi, Kenya, in February 1999 and an agreement is hoped for by 2000.

The next meeting will be held in autumn 1999 (*Chemical Market Reporter*, February 22, 1999). For more information see the POPs Homepage at http://irptc.unep.ch/pops/ or contact the UNEP Chemicals/POPs Team, Chemin des Anemones, CH-1219 Chatelaine, Geneva, Switzerland (Tel +41 22 979 9190 or 9171; FAX +41 22 797 3460; email pops@unep.ch).

ICI's safety, health and environment strategy

ICI's safety, health and environment strategy is supported by beliefs including the following:

- an injury and illness-free workplace can be achieved
- all losses of containment can be prevented
- performance is directly related to the levels of ownership
- ICI's market performance will mirror its product stewardship

The company believes that by building sustainability into its business strategy it will achieve competitive advantage. It has already gained advantage from the shift from solvent-based paints to water-based solvents. It produces these to high quality with no or greatly reduced levels of volatile organic compounds. ICI is a founder member of the World Business Council for Sustainable Development and it believes that it should be accountable to anyone with a legitimate interest in how it runs its business.

ICI has reported that its total waste volume is down by 15% compared to 1995 while over the same period production has increased by about 4%. Individual improvements include that of ICI polyurethane at its Dutch site where in a collaboration with Akzo they have reduced the site's emissions of carbon monoxide by 75%. Akzo takes an ICI by-product and combines it with excess carbon monoxide, which used to be released to the atmosphere, for use in its ethylene dichloride process.

New low-waste chloroalkali plants

Kvaerner Chemetics are to build two new low-waste chloroalkali plants for Orica in Australia. The plants will produce sodium hydroxide and chlorine. The Kvaerner processes will include recently patented technology to reduce waste discharges. (*European Chemical News*, 1999, **70**, 29).

QUILL rewrites the future of industrial solvents

"ULSTER Quill

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A MISCELLANY OF SHORT STORIES AND ARTICLES

Principal Contents:

WHAT IS THE FUTURE OF THE ULSTER THEATRE * JOSEPH TOMELTY & RUDDICK MILLAR

TELL ENGLAND * ULSTERMAN

THE NEW CURE * W. O. MURPHY

ROMANY ROMEO * THOMAS MADDOCK

VOICES IN THE BLACK-OUT * R. CARSON

THIS VALIANT SON OF ULSTER * S. NAPIER

FULL LIST OF CONTENTS INSIDE

BY ULSTER JOURNALISTS & SHORT STORY WRITERS

QUILL has earlier associations with Northern Ireland: this magazine was written 'by Ulster men and women for the people of Ulster'

Professor Ken Seddon of Queen's University, Belfast, and a co-director of QUILL reports on a successful collaboration in the area of ionic solvents

An industry–university collaborative research centre focussing on ionic liquids was officially launched at the Queen's University of Belfast (QUB), Northern Ireland at 12:30 pm on 20th April, 1999. Known by the acronym QUILL (Queen's University Ionic Liquid Laboratories), this novel Research Centre is the first to focus on ionic liquids in the world. Its structure is based on the successful QUESTOR (Queen's University Environmental Science and Technology Research) Centre (http://questor.qub.ac.uk/), which was set up in 1989, and won the Queen's Anniversary Prize for Higher and Further Education in 1996. Like QUESTOR, the new centre is based on the National Science Foundation's Industry–University Cooperative Research Centre (IUCRC) model.

There are seventeen founder industrial members of the QUILL consortium, and these are (in alphabetical order):

- Biopolymer Engineering (US)–Dr Doug Van Thorre
- BNFL (GB)–Dr Rob Thied
- BP Amoco (GB)–Dr Martin Atkins
- ChemVite (NI)–Mr Ted Wilson
- Chevron (US)–Dr Tom Harris
- DuPont (NI)–Mr Jim Wray
- Elementis (GB)–Dr Roy Laundon
- Exxon (US)–Dr Christian Mehnert
- ICI (UK)–Dr Andrew Burgess
- Merck (UK)–Dr Martin Pellatt
- Sachem (US)–Dr Roger Moulton
- Sasol (SA)–Dr Hein Strauss
- Schering Plough (I)–Dr Brian Brady
- SmithKlein Beecham (UK)–Dr Alan Curzons
- Solvay (B)–Dr Hans Meyer
- UOP (US)–Dr Paul Barger
- Zeneca (GB)–Dr David Moody

The chairman of the Industrial Advisory Board is Dr. David Moody of Zeneca, who took over the chairmanship of the Shadow Board from Dr. Graham Hutson (BNFL). The Centre's co-directors are Prof. Jim Swindall OBE (who also is director of QUESTOR) and Prof. Ken Seddon (who is an EPSRC and Royal Academy of Engineering Clean Technology Fellow).

ABOVE: *QUILL Industrial Advisory Board members (holding membership certificates) and QUILL directors with Professor Hogg (Pro-Vice-Chancellor of QUB; centre front.* ABOVE RIGHT: *Prof. Brian Hogg (QUB Pro-Vice-Chancellor for research) presenting Dr. David Moody (Zeneca) with his QUILL membership certificate.*

Dr. Sarah Thompson (neé Boyle; EPSRC Clean Synthesis Fellow) with an autoclave for preparing ionic liquids

So what are ionic liquids, and what have they to do with green chemistry? Clean technology concerns the reduction of waste from an industrial chemical process to a minimum: it requires the rethinking and redesign of many current chemical processes. As defined by Roger Sheldon, the *E*-factor of a process is the ratio (by weight) of the by-products to the desired product(s).[1]

Industry	Production /tons p.a.	E-factor
Oil Refining	$10^6 – 10^8$	0.1
Bulk Chemicals	$10^4 – 10^6$	1–5
Fine Chemicals	$10^2 – 10^4$	5–50
Pharmaceuticals	$10^1 – 10^3$	25–100

The Table illustrates that the 'dirty' end of the chemical industry, oil refining and bulk chemicals, is remarkably waste conscious: it is the fine chemicals and pharmaceutical companies which are using inefficient, dirty, processes, albeit on a much smaller scale. Volatile organic solvents are the normal media for the industrial synthesis of organics (petrochemical and pharmaceutical), with a current worldwide usage of *ca*. £4 billion p.a. However, the Montreal Protocol has resulted in a compelling need to re-evaluate many chemical processes that have proved otherwise satisfactory for much of this century. There are four main alternative strategies:

- solvent-free synthesis
- use of water as a solvent
- use of supercritical fluids as solvents
- use of ionic liquids as solvents

It is the purpose of QUILL to explore the last of these options, to allow it to be evaluated against the other strategies, and to demonstrate its viability for commercial development in all sectors of the chemical industry.

Thus, the principal aim of the QUILL programme must be to explore, develop and understand the role of ionic liquids as media for industrially relevant chemistry, and to provide all the physical and chemical engineering data necessary in order to facilitate the design and operation of a pilot plant. Ionic liquids possess, *inter alia*, the following desirable properties:

- they have a liquid range of 300 °C, allowing tremendous kinetic control
- they are outstandingly good solvents for a wide range of inorganic, organic and polymeric materials–high solubility implies small reactor volumes
- they exhibit Brønsted, Lewis, and Franklin acidity, as well as superacidity[2]
- they have no effective vapour pressure
- they range from hydrophobic to hydrophilic, from water-sensitive to air-stable
- they are thermally stable up to 200 °C
- they are relatively cheap, and easy to prepare[3-5]

Unlike water and other hydroxylic solvents, they will dissolve a wide range of organic molecules: exploratory work in our own laboratories (carried out in collaboration with BP Chemicals and Unilever) has demonstrated that a wide range of catalysed organic reactions (including oligomerizations, polymerizations, alkylations, and acylations) occur in room-temperature ionic liquids, and that these are serious candidates for commercial processes. The reactions we have observed represent the tip of an iceberg–all the indications are that room-temperature ionic liquids are the basis of a new industrial technology. They are truly designer solvents.

Examples of industrial relevance which have been developed over the past few years at Belfast include:

- Synthesis of poly(isobutene)[2]
- Friedel–Crafts chemistry[7]
- *N*- and *O*- alkylations[8]
- Diels–Alder chemistry[9]
- Isomerisation of fatty acids and esters [10,11]
- Nuclear fuel reprocessing[12,13]

To meet the synthetic challenges and comprehensive characterisation programmes, QUB is building a new suite of laboratories for QUILL, including state-of-the-art handling facilities. A team of at least ten researchers (comprising of postdoctoral fellows, technicians and graduate students) will start work in October 1999 on a four-year programme. The end result should be a generic ionic liquids database, and feasibility studies to enable the construction of at least two pilot plants.

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Chemical Educational Foundation—a network of resources

Searching for educational materials on the safe handling of chemicals? The Chemical Educational Foundation, a non-profit organization, located in Arlington, VA, USA, provides various publications, videos, and programs on chemical product stewardship targeted toward school children, chemical companies and their customers, emergency responders, universities, and the general public. The CEF's mission is to 'serve the public interest as a primary, national resource for conducting research and educational programmes on proper distribution practices for the safe handling, storage and transportation of chemical products'. Many of the Foundation's materials are free and can be downloaded from their web site (http://www.chemed.org)

What is chemical product stewardship? Chemical product stewardship is a management practice many chemical companies follow to ensure that health, safety and environmental protection becomes a part of a chemical product's life cycle. Product stewardship should be carried out in every stage when designing, manufacturing, marketing, distributing, using, recycling and disposing of chemical products.

The Chemical Educational Foundation (CEF) began promoting chemical product stewardship activities when it was founded in 1992 by the National Association of Chemical Distributors (NACD). The Foundation was established to raise industry, customer, and community awareness about the safe handling of chemicals. The Foundation utilized the NACD chemical distributor members' vast network of 750,000 customers and communities to communicate this important message and distribute educational materials. Six years later, the Foundation now reaches hundreds of thousands of businesses and several million individuals with the message of chemical product stewardship –a shared responsibility for everyone to safely handle chemicals.

The Foundation's successful outreach is attributed to the dedication of many chemical distributor and manufacturer Foundation sponsors. Other supporters of CEF, including the National Association of Chemical Distributors, Chemical Manufacturers Association, the Synthetic Organic Chemical Manufacturers Association, and the National Paint and Coatings Association, have also helped the Foundation fulfill its mission.

For more information contact The Chemical Educational Foundation, 1560 Wilson Boulevard, Suite 1250, Arlington, VA 22209, USA. Tel. +1 703 527 6223; Fax +1 703 527 7747, or visit the Web (http://www.chemed.org) to find more information about:

- **You Be the Chemist Kits–** two interactive, educational curriculums, one designed for K-3 and the other for 4–6 graders, teach students about chemistry and the safe handling of chemicals. Nearly 20,000 Kits have been distributed to schools with a total outreach estimated at nearly 1.5 million

The 1999 Vanguard Awards

The Chemical Educational Foundation in the USA has announced the recipients of the 1999 Vanguard Awards. These are G. S. Robins, President, G. S. Robins and Company and Past-President of the National Association of Chemical Distributors (NACD), and A. W. Tamarelli, Chairman and CEO of Dock Resins Corporation, and former Chairman of the Synthetic Organic Chemical Manufacturers Association (SOCMA). The award winners have been chosen for their efforts to nurture product stewardship relationships across all industries and communities served by the chemical industry. The Chemical Product Stewardship Awards finalists are in the three categories of Manufacturer Award, Distributor Award (in two categories of below and above annual sales of $25 million), and Community Award. The Vanguard Awards were presented and the Chemical Product Stewardship Award winners and Honourable Mentions announced at the Chemical Educational Foundation's banquet on 12 May 1999 in Washington DC.

New educational tools to teach school children about safe handling of chemicals and product stewardship students, teachers and parents. The new K-3 Kit was first shown at the National Science Teachers Association's National Convention at Boston in March 1999.

- **Product Stewardship Bulletins–** quarterly issues highlighting topics of interest to the chemical industry and the public. More than 1.2 million copies of the bulletins have been distributed to date. The Bulletins address many issues, including chemicals in your home, home chemical safety and emergency procedures, and EPA's Risk Management Program (RMP).

- **The HAZMAT Training and Regulatory Awareness Program–** a self-taught training program on DOT, OSHA, and EPA federal regulations. The CEF Regulatory Update Service provides subscribers with current updates on EPA, OSHA and DOT regulations affecting the chemical industry.

- **National Chemical Product Stewardship Week** ***(1-7 November 1999)***–this week is concurrent with the American Chemical Society's National Chemistry Week. During this week, chemical companies visit local schools or invite schools to tour their facilities so children, parents, and teachers learn more about how chemical companies handle chemicals and how chemicals effect our everyday lives.

European Solvents Stewardship award

The first European Solvents Stewardship award has been won by Irish pharmaceuticals producer, Irotec Laboratories. The award was presented by the European Solvents Industry Group (ESIG). The runners-up were Sun Chemicals (UK) and Hoogovens European Coil Coating Association (The Netherlands). Irotec produce bulk pharmaceuticals and active ingredients in Cork and its production capacity was almost doubled recently with the construction of a new multi-product production plant. In 1997 the company added three new tanks to store solvents and a solvent waste tank to its existing tank farm. This allows solvents, previously stored in drums, to be added directly into the production vessels. Thus solvent handling by operators and emission losses have been reduced. ESIG launched the awards in 1998 so as to promote and share best practice in the use of solvents. ESIG represents the producers of hydrocarbon and oxygenated solvents but not chlorinated solvents. An award scheme will again run for 1999 (*European Chemical News*, 1999, **70**, 32)

Factory Watch

Friends of the Earth (FOE) has used pollution data published by the Environment Agency to draw up a league table on its web site of Britain's worst polluters (http://foe.co.uk/factorywatch). Named 'Factory Watch' it aims to give people in Britain the chance to find out which major sources of pollution affect them, and which factories and companies are responsible. Factory Watch provides comprehensive information on the pollution and health risks from 440 chemicals from over 1500 factories across the country. Users can key in their postcode and find out the nearest 'filthy factory' or they can compile league tables of polluters by chemical, health hazard or industrial process. FOE claims to have made the first link between pollution data and potential health effects, although such links are impossible to prove. It calls for the government to set stricter emission reduction targets, to introduce comprehensive pollution inventories and to set up health studies around major sources of pollution. The Environment Agency is now calling for much larger penalties to be imposed to help cut down pollution; in 1998 the average fine for a prosecution was below £3000.

Green Chemistry Network

The GCN is growing in popularity, with our first newsletter being well received and new members joining on a daily basis. One particularly pleasing development is that we are now beginning to receive a number of enquiries from both members and non-members who have problems or issues they wish to discuss with others. Despite our still relatively small database we have be able to advise and put people, who would not normally have met, in contact with each other. The more information we have, the easier it will be to provide this networking resource so please contact us for a registration form.

The majority of our members are currently from academia, during the next few months we will be focussing our efforts to recruit more people from industry. It is only when green chemistry is put into practice by industry that the environmental, economic and social benefits will be seen. In an attempt to

Friends of the Earth

encourage industry to be more open about some of the exciting new green processes now being developed we are in advanced stages of negotiating the introduction of prestigious Green Chemistry Awards for both industry (including SME's) and people in education. We are keen to publicise the good things happening in industry, without disclosing any proprietary technology, so please get in touch.

We are arranging our first GCN postgraduate seminar for 28 September in York. The day will consist of presentations from postgraduates and postdoctoral fellows from local universities on several aspects of Green Chemistry followed by a plenary lecture from a leading expert in the field–in this case Ken Seddon from Queen's University in Belfast. We hope to organise these seminars all around the UK: please let us know if you would like to hold such an event.

Mike Lancaster (greennet@york.ac.uk)

The National Pollution Prevention Center for Higher Education (NPPC)

The National Pollution Prevention Center for Higher Education (NPPC) is based at the University of Michigan, USA, and has extensive resources of teaching and research materials for faculty (academic staff). These include case studies, resource lists with full texts available on line and compendia on subjects including chemistry, chemical engineering, industrial ecology, environmental studies and sustainable agriculture. The chemistry compendium includes a resource list of educational tools with reference material including numerous articles, reports, publishers, on-line services and the names of individuals and organisations involved in pollution prevention education. Additionally the compendium includes access to a thesis on the Incorporation of Pollution Prevention Principles into Chemical Science Education. This thesis includes a review of the literature on green chemistry and a proposed methodology for chemical life science analyses that can be incorporated into University-level chemistry curricula.

For further information contact the National Pollution Prevention Center, University of Michigan, USA. (http://www.umich.edu/~nppc.pub/resources)

Forum to discuss the Royal Commission report on Setting Environmental Standards

IChemE, the Institute of Chemical Engineers, organised an open forum in London on 7th April to discuss the report by the Royal Commission on Environmental Pollution on Setting Environmental Standards: The Challenge for Industry. The report has called for environmental policies and standards to be informed by rigorous and dispassionate analysis but also by greater sensitivity to people's values from the earliest stages of defining problems. It concluded that setting a standard is not only a scientific or technical matter but also a practical judgement which has to be made in the light of all relevant factors. The forum sought to cover the following issues:

- How does this thinking affect industry?
- How can scientists contribute most usefully in the regulatory context?
- Is there a case for new forms of environmental regulation?
- Would more self-regulation deliver better environmental protection at less cost?
- How can we develop processes to produce more acceptable and robust decisions, reconciling uncertainty and possibly conflicting objectives?
- Could life-cycle approaches make environmental standards more effective?
- Would greater use of risk analysis make standards more acceptable?

The Forum was opened by the Chairman of the Royal Commission on Environ-mental Pollution, Sir Tom Blundell. The Director of the Centre for Environmental Strategy at the University of Surrey, Professor Roland Clift, then gave an outline of the findings of the Commission. Professor David Taylor, representing the Chemical Industries Association, spoke on what the findings could mean to the process and chemical industries. Finally the Director of the Centre for the Study of Environmental Change at the University of Lancaster, Mr Robin Grove-White, addressed the social values in terms of what they are and how we should take account of them. There was then an open forum.

Grants for new ethanol technologies

The US Department of Energy (DOE) awarded $1 M to recipients of its 'Bridge to the Corn Ethanol Industry' initiative at the National Conference on Ethanol Policy and Marketing. The DOE initiative is designed to help expand domestic ethanol production by bringing together the established corn ethanol industry with newer technologies that produce ethanol from agricultural and forest wastes and other types of biomass. The cost shared grants, awarded through the National Renewable Energy Laboratory, are aimed at facilitating the production of ethanol from corn stover, which includes the leaves, stalks and cobs left over when the corn plant is harvested. The utilization of corn stover will increase the number of economical feedstocks available to ethanol producers. DOE granted $0.126 M to Vogelbusch USA Inc, Houston, TX, and Chief Ethanol Fuels Inc, Hastings, NE, $0.174 M for Purdue Research Foundation, West Lafayette, IN, and Williams Energy Services, $0.174 M for Ethanol, Pekin, IL, $0.155 M for Swan Biomass Co, Oakbrook Terrace, IL, and Chippewa Valley Ethanol Co, Benson, MN, $0.193 M for Merrick and Co, Aurora, CO, and High Plains Corp, York, NE, $0.188 M for The New York State Technology Enterprise Corp, Rome, NY, and Robbins Corn & Bulk Services, Sackets Harbor, NY, and $0.181 M for Swan Biomass Co, Oakbrook Terrace, IL, and High Plains Corp, Portales, NM.

Know of any green chemistry activities?

If you have any items relating to green chemistry initiatives, funding opportunities or regulatory activities which could be included in the 'Forum' section of *Green Chemistry*, please send them to James Clark or Duncan Macquarrie [email: greenchem@york.ac.uk; Fax: +44 (0)1904 434533 or +44 (0)1904 423559].

The significance of green chemistry to specialised organics SMEs

Christopher Drew from SORIS claims that the specialised organics sector is the original 'green chemistry'

Specialised organic chemical companies are 'green' pioneers. Their early roots lie in converting wastes from coal, steel and town gas into valuable soaps, dyes and disinfectants. Some company names (British Tar Products and Lancashire Tar Distillers) survive from these times but processes and products have changed, as have the prices and sources of raw materials.

Output maximisation models

Raw materials are now purchased in global markets and companies must accept the price as a fixed cost. Similarly, finished product prices (especially for specification chemicals) have hitherto been largely outside the influence of manufacturers.

Fig. 1 models this situation very simply. Individual companies succeed by the efficiency of their production processes (yield, batch time, energy usage *etc.*) in maximising output. They remain, however, at the mercy of raw material costs and finished goods prices.

This model highlights the chemical process as the only point at which companies can seek competitive advantage and explains the industry's search for new and more efficient technologies including photochemistry, ultrasound, microwave chemistry, supercritical fluids, ionic liquids and biotechnology. This search is complicated by the limited cash resources available to small- and medium-sized enterprises (SMEs). Companies can afford only one 'technology bet': and even this must be weighed against alternatives of a different nature—a marketing offensive, opening a new territory, joining a trade mission or investing in laboratories.

> 'effluent is money down the drain'

In the early 1980s NEDO (National Economic Development Office) suggested waste minimisation as a further means of improving performance and competitiveness, arguing that 'effluent is money down the drain'.

- it costs money to remove or treat effluent
- work is expended to convert raw material into effluent
- saleable material may be lost with the waste

Waste minimisation seemed to NEDO a logical money saver.

Industry initially rejected these arguments claiming that no problem existed, costs were negligible and waste streams were totally under control. It was a decade before NEDO published the Braithwaite Task Force report, 'Chemistry for a Better Environment', which recognised environmental issues as potential opportunities not threats. Companies agreed that waste was increasingly unacceptable and considered strategies for dealing with it. In increasing difficulty, cost, time-scale, efficiency and desirability these included:

- end-of-pipe solutions (for cleaner effluent)
- better process control and recycling (for less effluent)
- better process design (for even less effluent)
- alternative processes (to eliminate waste altogether)

The last two options are at the heart of what is now considered as 'green chemistry'.

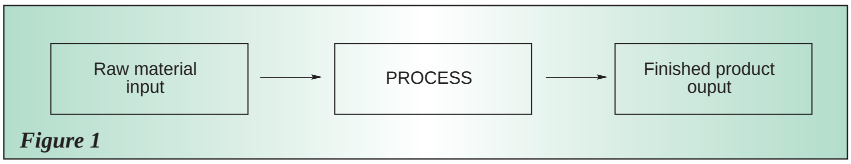


Figure 1

SORIS

SORIS is a networking service from the Specialised Organic Sector Association (SOCSA), itself part of the UK Chemical Industries' Association (CIA).

SORIS offers 'soft' chemical information, helps companies solve problems, and provides tailored introductions. It collects information in a discreet and confidential manner and gives its subscribers :

- **extra 'antennae' in the marketplace**
- **longer business development arms**
- **wider horizons**
- **quick information**
- **time savings**
- **new opportunities**
- **specialist introductions**
- **anonymity**
- **interpretation of 'grey' information**

SORIS was established in 1980 and became part of the CIA in 1993. It is a non-profit body, funded by the chemical industry but able to offer services to customers outside the immediate chemical industry. Its remit is to provide 'information which subscribers cannot readily or easily obtain for themselves', and hence, in a sense, SORIS is an industrial dating agency.

For further information on SORIS contact Christopher Drew at SORIS, Macclesfield (Tel. +44 (0) 1625 618439; FAX +44 (0)1625 511336; email cdrew@soris.demon.co.uk) and from http://www.sourcerer.co.uk/html/english/soris.htm.

For further information on SOCSA contact Tony Scott, SOCSA Director at CIA (Tel. +44 (0)171 963 6716; email scottt@cia.org.uk).

The simple industry model now looks like Fig. 2.

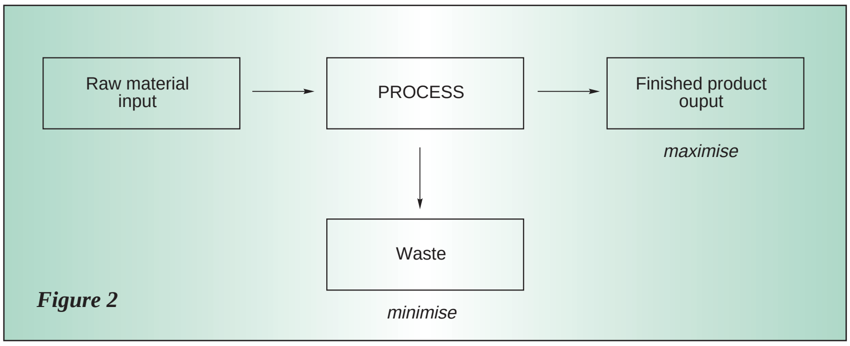


Figure 2

The difference between Figs. 1 and 2 represents an attitude change, driven by the costs of a 'licence to operate'. The UK specialised organics sector is reckoned to have an annual turnover of £6bn. Aggregate UK chemical industry statistics show capital spending at 10% of turnover. Applying this ratio to specialised organics suggests that £600m is invested each year. Anecdotal reports describe 50% of capital spending as 'defensive', by which they mean it is not directly productive but is essential to anticipate environmental requirements. This means that £300m pa is unavailable for investment in R&D, product and process development or new processes.

> 'better process design and alternative processes are at the heart of green chemistry'

Revenue maximisation models

Other impacts are much more direct, though difficult to measure. Chemical manufacturers require authorisation from HMIP (Her Majesty's Inspectorate of Pollution) to operate chemical processes. Authorisation is granted for 'processes' and 'components'—with a fee payable for each item. A small company with the capability (and desire) to operate a wide range of batch reactions pays a very heavy price for authorisations. By contrast a large company, operating a few, continuous, processes pays relatively little. These costs serve to reduce companies' responsiveness to demands for custom and toll manufacture. Further, the time and effort taken to gain authorisation for a new activity for the market adds to development costs and extends product lead times by 2 to 3 months. Examples exist of UK companies losing overseas business as a direct result.

Whilst, on one hand, the costs of remaining in business increase, on the other, companies are better at recognising their (previously under-valued) worth to their customers. Specification chemicals are like commodities in the marketplace. Price differentiation is possible, but not easy. Performance or effect chemicals are targeted more precisely at market needs. Customers (except for pharmaceuticals and agrochemicals) are not interested in molecular structures: they want flavour, aroma, texture, colour, absence of dirt or bugs and so on. With additional service or flourishes (door to door delivery, technical service representatives), pricing can be very specific to a customer–supplier relationship. Thus chemical manufacturers can regain influence over their product revenues.

Adding these two drivers (increased process control and greater market sensitivity) to the model produces Fig. 3.

Here, companies' goals have subtly changed from output maximisation to revenue maximisation. Manufacturers of expensive perfume do not necessarily double their income by doubling their output. If scarcity and exclusivity are lost prices will likely fall–and the effect on revenue is a tricky judgement. Not all chemical sectors behave the same but companies are more aware that profitability is a function of price and output–not volume alone. Case studies abound (mostly outside chemicals!) of companies chasing output targets and seeing their losses rise accordingly.

Intangibles

An apocryphal President of a US cosmetics company said 'we make chemicals but we sell hope'. His analysis was deeper than the specification–effect dichotomy. He recognised that customers buy intangibles as well as effects. This might be peace of mind from dealing with a known, reputable supplier; it might be protection from aggravation by outsourcing a whole activity instead of

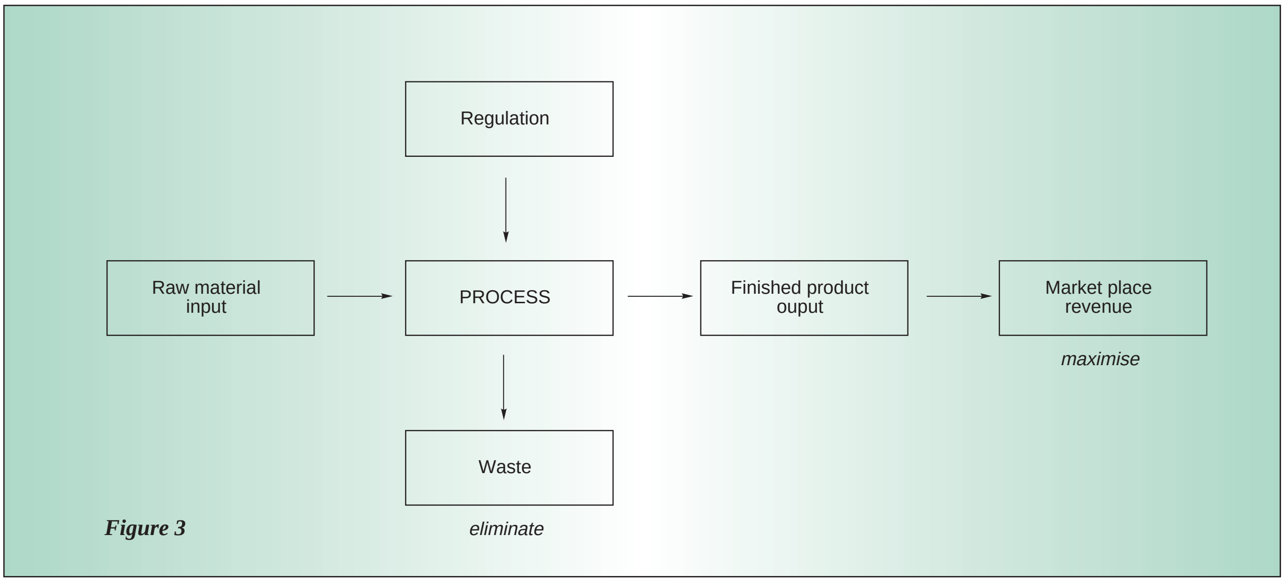


Figure 3

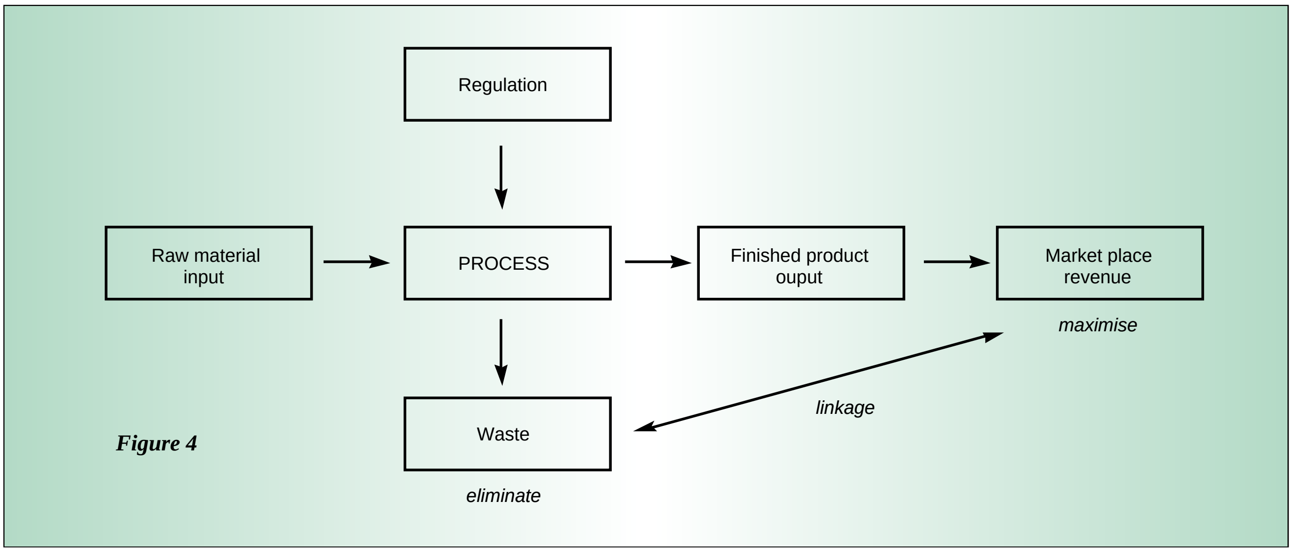


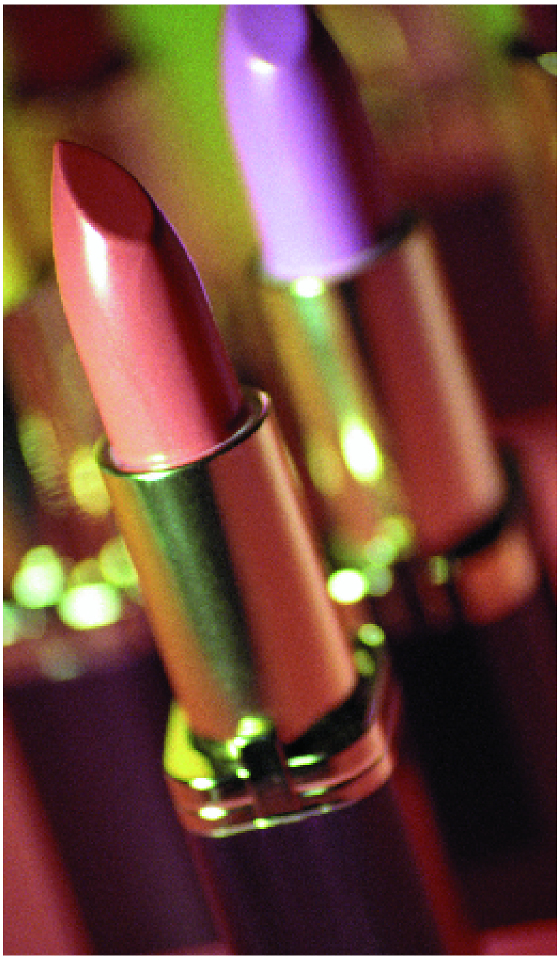
Figure 4

components; it might be confidence in uninterrupted supply.

These intangibles have a value, which should be reflected in the price (of the chemicals). Leading specialised organics companies are beginning to address this issue of value pricing. Whether pricing is a science or an art, it is difficult in these circumstances. Companies are rewarded by less buffeting by external influences and more control over their business environment. An increasingly important intangible (though stronger in consumer than industrial markets) is market perception of a company's environmental performance.

Adding this linkage between environmental and market performance to our model leads to Fig. 4.

Strictly Fig. 4 is a qualitative description with no predictive power. It perhaps suggests lines of academic research on the nature and strength of the posited links. Such work should be aided by the Integrated Pollution Prevention and Control (IPPC) requirements (due to come into force on 30 October 1999) for companies to report energy and raw material usage in their operations. Chief executives have developed their own rules of thumb for balancing the relative effort put into R&D, marketing, finance an personnel. 'Environment' is a business topic that currently absorbs all available effort–and more. Guidance on its place in the total business dynamic would be valuable to companies.



Speciality chemicals industries like the cosmetics industry are aware that maximising revenue depends on many intangible factors, such as exclusivity and environmental performance.

Conclusion

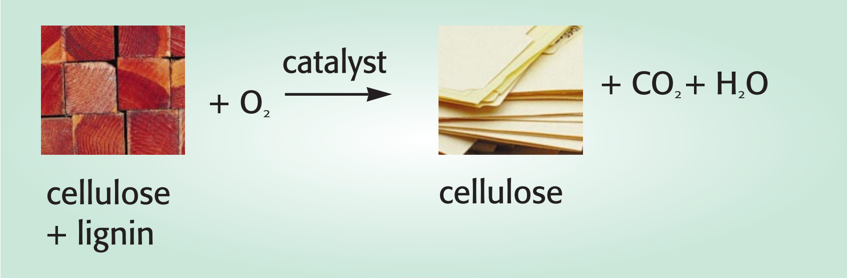
I claim that the specialised organics sector is the original 'green industry'. There are current strong drivers (cost, legislation and market) which make waste minimisation an major part of companies' business strategy. A good start has been made at 'end of pipe' solutions and steady upstream progress is being made. Companies are keenly interested in technologies and processes with a green chemistry cachet, but implementation will not be immediate. Companies in this sector tend to be small (or to be small and relatively free-standing subsidiaries of larger companies) and to have considerable variety and complexity in their operations. This limits the money and manpower that can be addressed to a single issue: it means also that 'one-size-fits-all' solutions are unlikely to exist for a range of problems.

The specialised organics sector has a strong history of collaborative R&D efforts and companies are working with each other to obtain better leverage on common projects, typified by the excellent and ambitious SETT project (SOCSA Effluent Treatment Toolkit) which is working towards the unambiguous goal, that early in the net millennium this sector's effluent streams will be of drinking water quality.

Further Reading

'Braithwaite Report'– The Chemistry for a Better Environment, National Economic Development Office, March 1992. ISBN 0-7292-1046-4
'Bringing in Integrated Pollution Prevention and Control' (Environment Agency) (http://www.environment-agency.gov.uk/files/tec_gui_ippc.htm)

Wood to paper without pollution



A completely new approach to use of oxygen in the bleaching of wood or wood pulp for paper manufacture has been developed by Craig Hill based at Emory University in Atlanta (email chill@emory.edu) and Ira Weinstock based at the USDA Forest products laboratory in Madison (email iaweinst@facstaff.wisc.edu). The method is based on the use of polyoxometalates which are nontoxic and inexpensive. In the first step the wood pulp is bleached by reaction with the oxidised polyoxometalate causing oxidation and solubilisation of the lignin leading to high quality cellulose fibres. In the second step, dioxygen is added and the same polyoxometalate catalyses the complete conversion of the lignin fragments to carbon dioxide and water. Overall the lignin has been removed from the wood using only air and water.

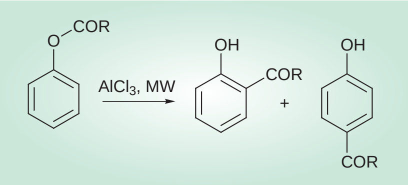
This represents a significant environmental improvement over chlorine-based processes. Its ‘green credentials’ include:

- less consumption of raw materials (wood) through higher process selectivity
- energy-efficient
- complete elimination of waste streams
- few greenhouse gases (CO_2)

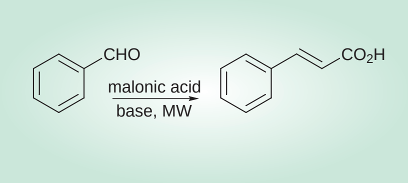
The new technology has been described in a series of U.S. patents and several research articles including an overview article published in *Holzforschung*, 1998, **52**, 304.

Microwave-mediated syntheses

The use of microwaves as an alternative reaction methodology has provided many useful synthetic protocols. For a recent review see R. S.Varma (*Green Chem.*, 1999, **1**, 43). Two recent publications extend the scope of this valuable technique. The first, from Bhushan Khadilkar at the University of Mumbai describes the Fries rearrangement at atmospheric pressure, avoiding the potentially hazardous use of sealed tubes (*Synth. Commun.* 1999, 1195). Results are good, often being better than conventional routes. Selectivity is similar to conventional heating, and generally delivers both *ortho* and *para* products

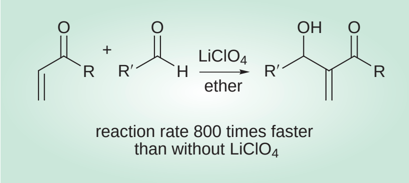


The application of microwaves to the Doebner condensation led Kumar’s group at the University of Calcutta to an improved method for the synthesis of a range of cinnamic acid derivatives (*Synth. Commun.*, 1999, 575). Yields are very high (94–97% for a series of differently substituted examples) and reactions are complete in a few minutes. The products are of use in the synthesis of lignans.



Improved Baylis–Hillman reaction conditions, a step in the direction of green chemistry

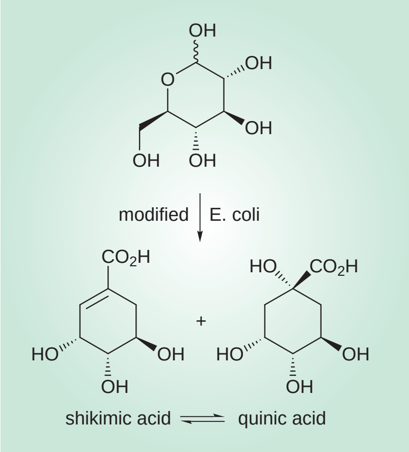
The Baylis–Hillman reaction is one of the most important synthetic reactions in organic chemistry, leading in one step to very highly functionalised products, which are of great synthetic utility. It is also an addition reaction, and thus does not generate co-products, making it potentially very clean. However, reaction times can be long, even with large quantities of base catalyst. Shu Kobayashi (University of Tokyo) has developed an improved set of reaction conditions, where the reaction proceeds 800 times faster when $LiClO_4$ is added to the system (*Tetrahedron Lett.*, 1999, **40,** 1539).



While the addition of $LiClO_4$ is not inherently green, the rate enhancements are particularly striking, and address one of the weakest points of the Baylis–Hillman reaction. More interestingly still is the possibility that ionic liquids might have a similar effect—Ken Seddon’s group at Queen’s University, Belfast, UK, has recently shown that the use of ionic liquids based on 1-butyl-3-methylimidazolium salts (bmim) gives rate enhancements in Diels–Alder reactions of a magnitude similar to those found when $LiClO_4$ is used, representing a cleaner alternative in this system (*Green Chem*., 1999, **1**, 23).

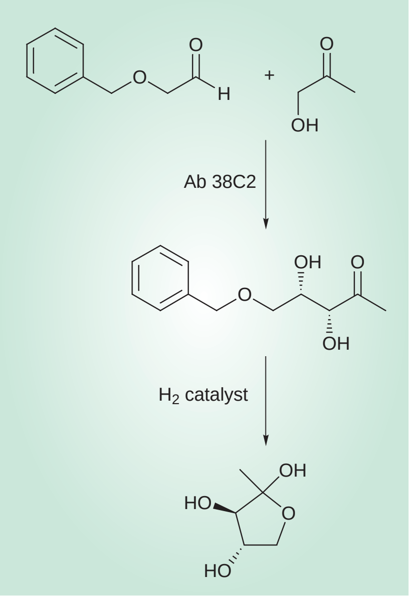
Microbes and antibody catalysis

Biotechnological syntheses of some biologically interesting molecules have been reported by two groups using different aspects of biotechnology. J. W. Frost’s groups at Michigan State University have prepared shikimic acid and quinic acid using recombinant microbial catalysts (*J. Am. Chem. Soc.*, 1999, **121**, 1603). The two acids are of great current interest as starting materials in the synthesis of potential influenza treatments. The group showed that both



materials are formed from D-glucose, and that the proportions of each was controllable by the glucose feed rate, the two acids being in equilibrium with each other. Control over the rate of addition allows the synthesis of either of the two acids.

The groups of Lerner and Barbas III at the Scripps Research Institute have developed a short route to 1-deoxy-L-xylulose using antibody Ab 38C2 (*Tetrahedron Lett.*, 1999, **40,** 1437). The two-step synthesis is the shortest yet devised, and relies on the fact that the antibody used does not require that the hydroxyacetone starting material is protected, thus contributing to a reduction in the waste produced by minimising protection/deprotection strategies:

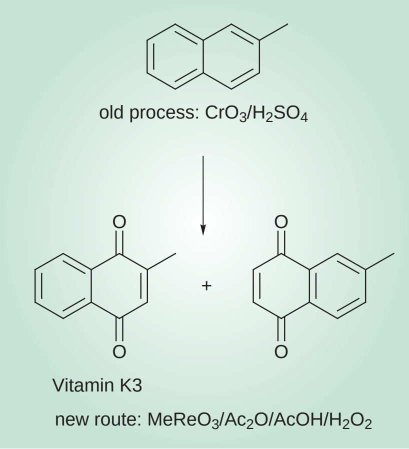


Clean Oxidations

Vitamin K3

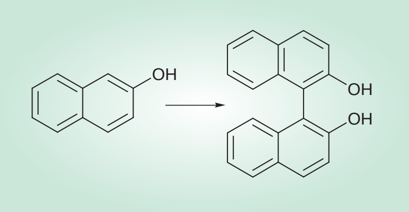
The synthesis of Vitamin K3 has long been a target for green chemistry. It is currently produced industrially by the oxidation of 2-methylnaphthalene by chromium trioxide in sulfuric acid. The use of such a stoichiometric oxidant generates a great deal of waste, and is becoming increasingly disfavoured by legislation. Many attempts to develop new, clean routes to this important molecule have been investigated, including a zeolite catalysed methylation of 1-naphthol by methanol, followed by bio-hydroxylation. Recent work by Hermann *et al.* at the Technical University of Munich (*J. Mol. Catal. A*, 1999, **138,** 115) has described an alternative approach.

They used the oxidation catalyst methylrhenium troixide, which has been shown to be applicable to the oxidation of alkenes and arenes, as well as in the Baeyer–Villiger reaction. The primary oxidant system was acetic anhydride/acetic acid and hydrogen peroxide, generating acetic acid as by-product. The authors showed that the combination of anhydride and acid was vital in terms of both activity and selectivity. Under optimum conditions, regioselectivity towards the methyl substituted ring oxidation was 89%, a very impressive result, and better than many of the other systems studied.



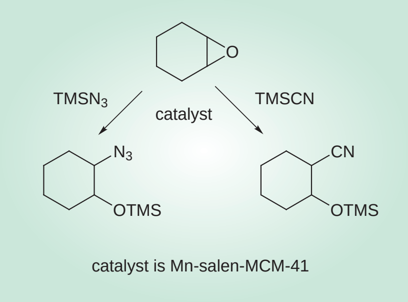
Binaphthols

A different oxidation of naphthalene derivatives is important in the synthesis of binaphthols, of much current interest as planar chiral catalyst precursors. Again, the current methods utilise stochiometric (or greater) quantities of transition metals as oxidants, typically those with a one electron redox system (*e.g.* Fe, Cu, Mn). Their use generates both metal waste and halide waste. Tong-Shuang Li and co-workers from Hebei University, Baoding, China, have developed a new catalytic route to binaphthols, where the primary oxidant is air (*J. Chem. Soc., Perkin Trans. 1*, 1999, 291). They used heterogeneous catalysts such as iron(III) chloride supported on alumina; while other systems were investigated, they were found to be less active. Yields are typically around 90% after several minutes in refluxing xylene. The authors showed that the oxidation proceeded stoichiometrically in the absence of air, but was catalytic in its presence. Catalyst recovery is simple, and successful reuse has also been demonstrated.



Elaboration of oxidation products

While the search for clean oxidation systems continues apace, most of the products of oxidation are used as raw materials in subsequent transformations. One of the most versatile classes of oxidation products is the epoxides. Two derivatives which are of importance in the synthesis of a range of biologically important compounds are cyanohydrin trimethylsilyl ethers and azidosilyl ethers. These two groups of compounds can be transformed into many important classes of compound, and their clean preparation is therefore desirable. Lakshmi Kantam and his groups from the Indian Institute of Chemical Technology have published results (*Synth. Commun.*, 1999, 1121) on the synthesis of these derivatives using Mn-salen complexes immobilised inside mesoporous materials, specifically MCM-41. These are designed as replacements for the more traditional catalysts such as homogeneous Lewis acids (*e.g.* zinc chloride). Both racemic and chiral salen complexes were investigated, but no enantioselectivity was seen.

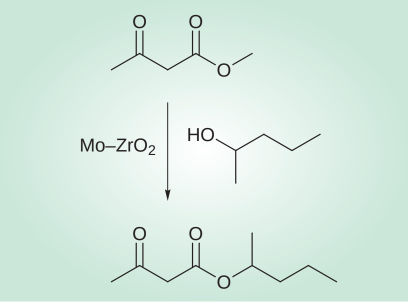


Transesterification catalysis

Transesterification is an important method for the preparation of many compounds. Major application areas include synthetic lubricants and surfactants. In many of these applications, the removal of a homogeneous catalyst (*e.g.* sulfuric acid) with water is a major problem, since the catalyst will also encourage hydrolysis. If the product has to be acid-free (often the case) this means that product isolation is extremely difficult, and leads to a great deal of waste in addition to the spent acid. Solid acids are therefore of great interest as replacements, both in terms of waste minimisation and product quality.

Thus, Benjaram Reddy *et al.* (Indian

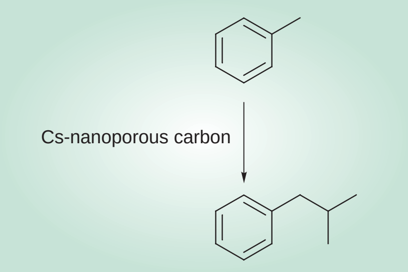
Institute for Chemical Technology) have developed Mo-zirconia catalysts for the transesterification of β-ketoesters (*Synth. Commun.*, 1999, 1235). The catalyst is effective with a number of alcohols, both linear and branched giving good yields of product. Separation and reuse of the catalyst can be achieved without loss in activity.



Novel solid bases

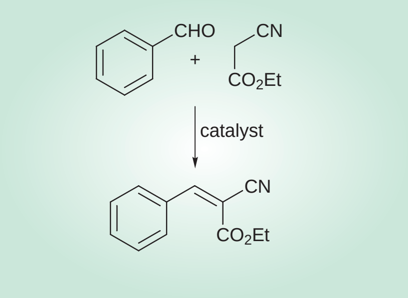
Caesium supported on carbon

The alkylation of toluene at the methyl group is a reaction of great importance, for example in the synthesis of isobutylbenzene, an intermediate in the synthesis of ibuprofen. Henry Foley and his team from the University of Delaware have just published details of a new catalyst system based on caesium supported on carbon, which is highly active in this reaction (*Chem. Commun*, 1999, 413). Previous work on intercalated graphites had led to materials with some activity, but requiring forcing conditions or long reaction times. Foley's team has used nanoporous carbon (NPC) to immobilise caesium, and found that, not only did it provide very good dispersion of the metal, but that its catalytic activity was also excellent. Gas phase reaction of toluene and propene takes place at 150 °C, a remarkably low temperature, and with very good selectivity. Higher temperatures lead to lower selectivity and catalyst deactivation



Quaternary ammonium hydroxides supported on siliceous MCM-41

A second novel base, this time with nanoporous silica as support, has been prepared by Avelino Corma and co-workers in Valencia (*Chem. Commun.*, 1999, 593). They functionalised purely siliceous MCM-41 with quaternary ammonium hydroxides in a two step reaction. The supported quaternary ammonium hydroxide was evaluated in the Knoevenagel reaction of benzaldehyde and ethyl cyanoacetate. They found that the catalyst was most active in the absence of solvent, and under these conditions, the turnover numbers were also higher than in the presence of solvent. Rates were comparable to unsupported tetramethylammonium hydroxide, although more catalyst had to be used. Good results were also obtained in Michael and aldol reactions (itq@upvnet.upv.es).



Algal biomass as raw material for food and chemical industries

The Dutch company Algen Systemen UvA BV is developing a system for the large-scale cultivation of algal biomass on a substrate containing organic substances in a process which involves symbiosis with a bacterium. The latter generates carbon dioxide which is then assimilated by the algae *via* photosynthesis along with nitrogen and phosphate. The algal mass has prospects for use in commercial applications such as human health foods, animal feeds, the chemical industry, cosmetics, and pharmaceuticals. It can potentially be used to produce fine chemicals such as proteins (with a similar nutrition to that of soya), carbohydrates (industrial polysaccharides and fermentation substrates), lipids (particularly unsaturated fatty acids, hormone precursors, and surfactants), vitamins (high concentrations of vitamin B12), and pigments (*e.g.*, chlorophyll, carotenoids, and xanthophylls). This would represent an environmentally friendly method for producing natural fine chemicals. Fundamental research into the growth of mass cultures is being carried out at the University of Amsterdam where a number of so-called High Rate Algal Pond systems have been set up to determine the optimal conditions for cultivation, such as light intensity and nutrient levels.

Toluene-diamine recovery and recycling

Takeda Chemical Industries Ltd and Kobe Steel Ltd have jointly developed an environmentally friendly method to recover and recycle the toluene-diamine (TDA) residue generated in the production of tolylene diisocyanate (TDI) using supercritical water technology. A commercial-scale recycling plant based on the newly-developed technology at Takeda's Kashima Plant in Ibaraki Prefecture, northeast of Tokyo, has recently started commercial operation. (The Kashima Plant produces TDI for production of polyurethane resin.) This is the first time supercritical water has been used to recycle plastic intermediates on a commercial basis. Supercritical water is friendly to the environment as water serves as the solvent. No acids or alkalis are used, so waste water treatment is unnecessary.

Renewed boost for ethanol

With oil prices low and corn prices high, ethanol has found it hard to achieve commercial success as a renewable fuel. But biotechnology may provide help. Genetic engineering is coming up with bacteria that can produce ethanol from waste. BC International (BCI) is erecting a 20 M gal/year ethanol plant at Jennings, AL, that will use biomass as feedstock and a genetically-modified bacterium. BCI expects to produce ethanol for $1.20/gal or less. In the UK, Agrol Ltd expects to begin designing a demonstration plant for converting waste to ethanol by the end of 1999. It hopes to use waste recovered from the upgrading of sugars and starches, as well as straw and forestry wastes. Masada Resource is to begin construction of an 8 M gal/year waste-to-ethanol plant at Middletown, NY, in spring 1999. US ethanol output was 1.36 bn gal in January–October 1998. A number of facilities are due onstream in 1999, including Exol's 30 M gal/year unit at Albert Lea, MN; Adkins Energy's 30 M gal/year plant at Lena, IL; and Sunrise Energy Ethanol's 5 M gal/year unit at Blairstown, IA. Heartland Grain Fuels is erecting another 8 M gal/year plant at Aberdeen, SD.

Clean Technology Programme

Tim Lester describes a programme run by the UK Research Councils in the early 1990s

Introduction

The Clean Technology Programme owed its origins to a number of enthusiasts working in, and associated with, the UK Science and Engineering Research Council (SERC).Two key players were Professor Roland Clift and Dr Nicholas Lawrence.

Professor Roland Clift, currently Professor of Environmental Technology and Director of Centre for Environmental Strategy at the University of Surrey, was a key player in the Clean Technology Programme

Professor Clift of the University of Surrey was Chairman of the SERC's Process Engineering Committee. Dr Lawrence became the SERC's Director/Senior Programme Manager and assembled a small team of staff within SERC to help him establish and manage the programme.

The first meeting of a working party, chaired by Professor Roland Clift, to define a possible new SERC programme area on clean technology was held in August 1989. During that autumn a 'Forward Look' submission was approved by SERC Council and in 1990 the Clean Technology Programme was born. From early 1990 selected research proposals were part funded from a Clean Technology budget. The first meeting of the Clean Technology Management Committee was held in the autumn of 1990. The Management Committee was initially chaired by Roland Clift and included representatives from universities, industry and government. Dr Geoffrey Randall later chaired a group of external advisors who reviewed the programme.

Three studies were commissioned to examine different areas for their clean technology potential and the outcomes were the following 'research agenda' documents:

- Farming as an Engineering Process
- Harnessing Photosynthesis
- Clean Synthesis of Effect Chemicals

The Clean Technology Management Committee recommended that these subjects form the initial thrusts of the Clean Technology Programme. There was a press launch in February 1992.

The Clean Technology Programme was unusual–its funding was 'cross council' involving both SERC and AFRC.

In 1994 the Research Councils were re-organised and renamed. EPSRC (Engineering and Physical Science Research Council) took over most of SERC's responsibilities and BBSRC (Biotechnology and Biological Sciences Research Council) assumed many of the AFRC's. For the rest of this article the current Research Council names will be used.

This collaboration between Research Councils was not common when the Clean Technology Programme was launched and proved effective. Collaboration also took place within EPSRC with the Chemistry and Process Engineering programmes both contributing to the Clean Technology budget.

Scope of the programme

The principal aim of the programme was to fund high quality research with potential to contribute to cleaner, more sustainable technologies and, in the case of the cities programme, lifestyle.

The mechanism used was to fund research proposals submitted to the Research Councils by UK universities which met certain criteria for originality, relevance and quality. Commonly the research proposals were for 2–3 years with funding in the range £100–300k. The methods used to select proposals varied in detail between different parts of the programme and also over time. As usual for Research Council funding, peer review played an important role.

Some 20 Clean Synthesis ROPA (Realising Our Potential Awards) were made during the life of the programme. ROPAs differ from normal Research Council awards because to be eligible the applicant must be able to demonstrate substantial and recent collaboration with industry.

In addition to funding research, the Clean Technology Programme aimed to raise the profile of waste generation and sustainability within the wider community. This objective was addressed in several ways of which the following are examples:

- Royal Academy of Engineering/ EPSRC Clean Technology Fellowships were awarded to 10 active university researchers (see box below). These fellowships lasted for three years and during this time relieved members of academic staff from their teaching responsibilities. This allowed them to focus on Clean Technology Research, giving lectures and undertaking various 'public understanding' activities.

- Clean Technology PhD Studentships were awarded to academics on the basis

Royal Academy of Engineering–Clean Technology Fellowships

Name	Institution	Research Area
Dr T. Markvart	Southampton University	Photovoltaics
Professor M. Poliakoff	Nottingham University	Supercritical Fluids
Dr T. Jackson	Surrey University	Thermodynamics and Sustainability
Dr J. Rosenfeld	Cardiff University	Advanced Glazing
Dr D. Barrow	Cardiff University	Chemical Sensors
Dr P. Mitchell	Bath University	Mining and Mineral Processing
Professor K. Seddon	Queen's University Belfast	Ionic Liquids
Dr I. Dunkin	Strathclyde University	Photochemistry
Professor J. Clark	York University	Heterogeneous Catalysis
Mr D. Hicks	Bath University	Design for Decommissioning

of proposals covering the intended work programme and training which would be provided. These students were invited to a multidisciplinary Clean Technology Summer School, lasting three days at which there were talks by Clean Technology Fellows, a poster competition was held and various other activities took place.

- Publication of a newsletter: 'Cleanline' about twice a year which reviewed some research results, listed calls for proposals, awards made, *etc*.

EPSRC

CleanLine5

Goodbye to electricity bills and sulphur dioxide?

- Organisation of workshops bringing together university researchers and industry staff

- 'Blue Sky' calls to encourage unconventional ideas by providing small grants to allow preliminary feasibility to be assessed.

- Publishing a directory of research projects funded (last one was dated December 1996)

Constituent themes

The programme was expanded beyond the three initial themes to cover the following:

Farming as an Engineering Process
Funded by EPSRC and BBSRC, the objective was to investigate the potential for applying mathematical modelling, measurement and control systems, sensors, *etc*, to farming in order to optimise use of energy, chemicals and other resources.

Harnessing Photosynthesis–renamed Light Harvesting
Funded by EPSRC and BBSRC, this programme included:

- biological light-capturing processes
- aspects of photovoltaics
- light-driven hydrogen production from photosynthetic organisms
- aspects of photochemistry

Clean Synthesis of Effect Chemicals–renamed Cleaner Synthesis
Funded by EPSRC and discussed more fully below.

Fuel Cells for Clean Power Generation and Transport
Funded by EPSRC, this programme started in 1994.

Stopping Waste within Production Process–also known as WMR3
(*Waste **M**inimisation–**R**ecovery, **R**ecycling and **R**euse in industry*) Funded by EPSRC, programme started in 1994. A related LINK Programme (part of the UK Government LINK Scheme requiring 50% industry funding) was established on this topic.

Cities and Sustainability
Funded by the SERC/EPSRC and ESRC (Economic and Social Research Council).

Life Cycle Analysis
Funded by the SERC/EPSRC and ESRC.

In addition to these programmes which were managed by the Clean Technology Unit within EPSRC, financial contributions were made to other programmes which were relevant to clean technology objectives. Examples were 'Combustion', 'Catalysts and Catalytic Processes' and 'Materials for Better Construction'.

Timing

In common with a number of other Research Council initiatives, the Clean Technology Programme was a five-year programme. It was launched in 1992 and closed in 1997, although some awards continue to be made in a few subject areas. A number of the projects which started in 1997 are not scheduled to finish until 2000.

Cleaner Synthesis theme

In order to provide guidance to academic researchers it was necessary to identify and disseminate information on problems and opportunities facing the chemicals industry. This was done through discussions and a meeting at the SCI which was attended by about 100 industry and university staff. Views were sought on prospective topics for research and a

Main areas of research funded within the Cleaner Synthesis theme

Benign solvents

- supercritical fluids as straight alternatives to hydrocarbons but also to allow one to do things differently, for example controlling morphology during isolation of solids or giving different products when used as reaction media
- ionic liquids as both chemical reagents and involatile, recyclable solvents
- water as a medium for radical chemistry

Catalysis

- to find alternatives to aluminium trichloride in Friedel–Crafts reactions
- asymmetric synthesis–for oxidation, epoxides and aziridines; potential of polyleucine
- properties of novel solid acid heterogeneous catalysts
- use of computer modelling to help understand the selectivity of certain catalysts
- identification of heterogeneous catalysts for selective ethane oxidation

Electrochemistry

- biosynthesis using electrodes based on immobilised enzymes
- organic synthesis in water–side chain oxidation, carbonyl reduction, *etc.*
- studies of a cleaner route to calcium which avoids lead containing dross

Radical chemistry

- finding ways to exploit radical chemistry commercially by identifying alternatives to the use of initiators based on tin or other 'unclean' reagents

Reactor design

- a bioreactor for enzymic oil hydrolysis with few by-products
- membrane reactors to exploit reactions with unfavourable equilibria
- studies of bubble behaviour in electrochemical reactors and a pulsed flow reactor; both to improve the commercial prospects of electrochemical synthesis

number of generic areas agreed. These findings were incorporated in calls for proposals which were peer reviewed and ranked by a panel with industry and university membership.

Chemistry departments dominated the Cleaner Synthesis programme with about four times as many projects as chemical engineering departments and over ten times as many as biological science departments. Collaboration between departments was strongly encouraged where this was logical and in at least one instance has led to ongoing links between departments. A common criticism by the industry representatives of the review panels was the lack of process engineering input to proposals from chemistry departments.

The total value of projects funded was around £12 million.

Attempts to classify the 118 projects into technical topics - such as reactor design, supercritical fluids, catalysis, or electrochemistry are thwarted by the number of projects which span two or more categories. The box (previous page) lists some of the types of work which were funded.

A key measure of the success of the programme will be that some of the research eventually contributes to changes in industry's methods of manufacture, resulting in cleaner processes. This will not, however, be straightforward to assess because there will always be a number of R&D inputs to new processes making it difficult to isolate the role played by the Cleaner Synthesis programme. Furthermore, for competitive reasons industry may provide little information for some years.

Although a number of the projects have still not been completed, there are encouraging signs that a number of the outcomes are relevant to industry. There are already examples of:

- Commercialisation
- Patents being filed by industry
- Follow up research funding from industry, in some cases through LINK projects

Other themes

The influence of chemistry extends well beyond the Cleaner Synthesis theme, contributing in a substantial way to Waste Minimisation, Photovoltaics, Fuel Cells, Combustion, and Analysis and Sensors. The box on this page lists several project titles from each theme, selected to give an impression of the scope of themes other than Cleaner Synthesis.

Outcomes

Results of research funded through the Clean Technology Programme are published by the academic investigators in the normal way, although where appropriate investigators are encouraged to file patents and this may lead to some limited delay in publication. Several pieces of research which were part funded through the Cleaner Synthesis theme will be presented at the Royal Society of Chemistry's Annual Conference in April 2000.

For further information see the EPSRC website on http://www.epsrc.ac.uk

Examples of research funded by some themes other than Cleaner Synthesis

Waste minimisation

- New clean technology for direct zinc smelting
- Modified absorbents for low-temperature gas purification
- Catalytic upgrading of pyrolysis oils derived from biomass and waste
- Environmentally friendly yarn dyeing
- Conformation of molecules at interfaces and the relationship to emulsion stability

Fuel cells

- Development of improved membranes for solid polymer electrolyte fuel cells
- Construction of a 1kW solid polymer fuel cell
- Electrocatalytic studies of new anodes for solid oxide fuel cells
- Development of a methanol fuel cell for automotive power
- Diffuse imaging as a probe of local charged states on Pt-Ru electrodes

Combustion

- Prediction of the performance of engine exhaust systems with catalytic converters
- NOx formation in and emission from pulverised fuel flames
- Computation of kinetic data for combustion modelling
- Mercury speciation in waste incinerator emissions
- Fundamentals of the electrostatic atomisation and burning of oil sprays

Analysis and sensors

- New oxide materials as sensors for combustion control
- Novel selective piezoelectric sensors using polymer reagents
- High temperature thin-film conductance sensors for gaseous sulfur-containing species
- Infra-red fluorescence sensor for metal ions
- Analysis of pollutants by non-invasive laser induced scatter fluorescence

Photovoltaics

- The physics of quantum well solar cells
- Passivation of active defect states in CuInSe$_2$ and CuIn$_x$Ga$_{1-x}$Se$_2$ thin films

Waste minimisation–the Don Rother Dearne Project

Becky Allen reports on two dozen small-to-medium-sized companies in South Yorkshire which are on course to net over £1 million a year in savings through waste minimisation

Introduction

Rising from the Pennines, the rivers Don, Rother and Dearne flow east through one of the most heavily industrialised regions of Britain. From Barnsley south to Sheffield and Chesterfield the Don, Rother and Dearne river basins are dominated by many small metal processors, as well as a few larger steelworks and chemical companies. Aiming to reduce emissions to the air, land and water by promoting cleaner production through waste minimisation, the Don Rother Dearne project ran in two phases between May 1996 and March 1998. It is the latest in a series of over 50 similar schemes run by the Centre of Exploitation of Science and Technology (CEST), local authorities and other organisations across the UK.

The Don Rother Dearne Project

This project involved 24 companies, including 18 small- and medium-sized enterprises (SMEs). The companies contributed almost 40% of the £207,675 total project costs, the rest being met by the BOC Foundation for the Environment, the Co-operative Bank, the Environment Agency and Yorkshire Water Services. Individual contributions ranged from £50 for SMEs that joined the project during phase 2, to £19,800 from Rhône-Poulenc, and it was its focus on SMEs that made the project special, says CEST, which coordinated the project.

> ‘a more focused approach to waste minimisation is required by SMEs’

Not only are they major businesses as well as polluters in the region, SMEs are also a difficult sector to recruit to waste minimisation projects because they frequently lack time and motivation. According to CEST: ‘For SMEs a quicker, more focused approach to waste minimisation is required than with larger companies, and the potential is generally less in percentage terms.’

Despite this, the Don Rother Dearne Project has achieved impressive results, particularly among the SMEs. It has identified potential financial savings totalling £1,079,918 per annum, about £500,000 of which involved no capital cost, the remainder having a payback of under a year. Although the financial savings were greatest in the larger companies–Rhône-Poulenc identifying savings of £96,000 a year–SMEs achieved percentage cost savings as high as the large firms.

For the environment this represents reductions of 5100 m^3 solid waste to landfill and 4500 tonnes of CO_2. The Environment Agency told *Green*

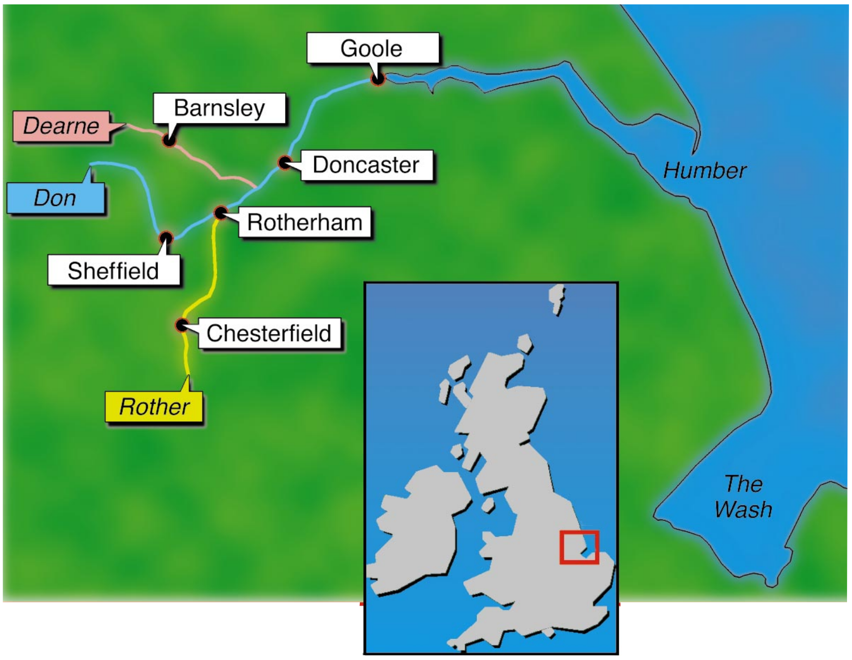
CEST–The Centre for Exploitation of Science and Technology

CEST is a not-for-profit organisation based in London, UK, with around 30 members drawn from:

- **industrial manufacturing and service sector corporates**
- **research and academic institutions**
- **government bodies and agencies**

Its mission is to ‘identify new business opportunities for science and technology and to assist their realisation by linking key decision makers in industry, research and development, helping them to identify the best options and to profit through collaborative action’. CEST operates through Collaborative Programmes, independent research sponsored by members, and other initiatives, based around areas where science and technology has the capacity to make big impacts, on business models and society in general.

For further information visit the CEST website (http://www.cest.org.uk



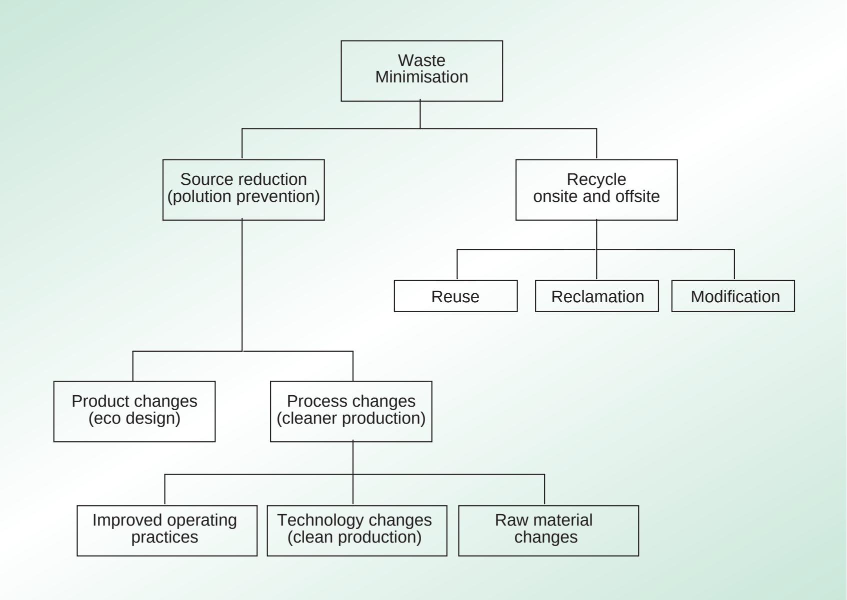
Chemistry: ‘There has been considerable success in water quality improvements in the rivers Don, Rother and Dearne over the past five years. These improvements have been brought about by a series of pollution prevention measures and through investment in a number of sewage treatment works. The river Don now supports a thriving coarse fishery and a local angler caught a 12 pound salmon– the first to be caught in the river for 150 years.’

Keys to success

CEST says several factors account for the project's success, but stresses that choosing a firm of consultants with past experience of working with SMEs to operate the project was critical. As well as taking an approach that is structured and specific to SMEs, senior management commitment and workforce involvement are vital, according to CEST. The project also identified a similar set of factors within companies that are often associated with problems making progress in waste minimisation. Most important among these is inadequate resourcing, particularly in the form of staff time. ‘A lack of suitable resources is more likely in smaller organisations, but absence of commitment to make them available can exist in any organisation’ CEST says.

Don Rother Dearne waste minimisation project methodology

- **Agree scope of work– organisation, team members, targets and third-party requirements.**
- **Agree resourcing and participant/consultant management system.**
- **Establish and train site-specific project team.**
- **Audit waste generated to air, land and water.**
- **Set policy, priorities and targets for reduction, as well as options for feasibility studies.**
- **Select and implement opportunities from feasibility studies.**
- **Management review to identify key changes required.**
- **Design and implement monitoring and targeting system.**
- **Establish project proposal system to develop, implement and evaluate future proposals.**



> ‘progress in waste minimisation is often limited by inadequate resourcing’

Many of the project participants identified workforce involvement as vital for success. Not only does this approach foster teamwork and ownership, it makes use of workers’ knowledge. ‘Although technology changes can be imposed, changes to working practices are more likely to be successful if suggested by those directly involved . . . Ideas generated by those close to the problem tend to be more pragmatic,’ says CEST. Integrating the waste minimisation with other management systems in the business is also important, not least because it minimised the additional staff time involved, a concern voiced by several firms before the project began.

Achievements

Two of the larger companies involved in the project were Rhône-Poulenc and Ronseal. Rhône-Poulenc operates a sulfuric acid, chlor-alkali and small pharmaceutical plant at Chesterfield and among the £96,000 a year savings identified was the replacement of demineralised water with towns supply. Richard Maylia, Environment Manager at Rhône-Poulenc's Chesterfield site, decided to become involved in the project because the company’s Leeds site, had benefited from a similar scheme in the past. Maylia’s main aim was to use the project to develop environmental management systems on site. Like many of the smaller companies involved, time constraints were a major problem: ‘It's not something for nothing, but if you have the time and commitment, then it is very worthwhile,’ Maylia says.

Ronseal makes consumer woodcare products at its Chapeltown plant in Sheffield and identified eight waste minimisation opportunities with potential savings of £122,000 a year. A significant proportion of this was achieved by changing production practices so that coloured products are made as clear intermediates and tinted in small, mobile vessels. As a result production lines require less cleaning, and £33,000 a year will be saved in cleaning materials and effluent treatment.

Two of the SMEs involved in the project were McKenna Precision Casting at Dinnington, and metal finisher

Example waste minimisation opportunities identified by project participants

- **Replacement of demineralised water with town supply**
- **Change of production practices so that coloured products are made as clear intermediates and tinted in small, mobile vessels**
- **Improvement of mould design and finishing operations, as well as reclaiming waste, to reduce the high-value alloy waste generated**
- **Reduction of chemical losses occurring in rinsing tanks**

R. Wilson & Co in Chesterfield. McKenna achieved savings of over £25,000 a year by improving mould design and finishing operations, as well as reclaiming waste to reduce the high-value alloy waste it generates. Wilson changed its chrome plating process to cut chemical losses that were occurring in its rinsing tanks, changes that cost nothing and saved £8450 a year. According to McKenna's Environment Officer Darryl Claytor the project acted as a catalyst and has left a lasting impact on the company, with waste minimisation objectives reviewed and revised annually. 'Being involved in the project made us aware of how we could make savings and concentrated our efforts,' Claytor said.

Whether there will be similar projects in the future is uncertain. CEST points out that the business case for waste minimisation has been made, and it is up to industry and policy makers to respond.

Further reading

Centre of Exploitation of Science and Technology (1998). The Don Rother Dearne Waste Minimisation Project Final Report, available from CEST [Tel: +44 (0)171 354 9942].

McKenna Precision Casting from Dinnington in South Yorkshire is an example of an SME which has been involved in the waste minimisation Don Rother Dearne Project.

Understanding Our Environment
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3rd edition
EDITED BY R. M. HARRISON

Reviewing 2nd edition
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The National Chemical Laboratory (NCL) at Pune, India. NCL's aim to develop green technologies using clean chemistry is aided by its creativity in catalysis.

NCL Golden Jubilee Catalysis Conference

Subramanian Sivasanker from the National Chemical Laboratory at Pune in India describes the start of a year of celebrations

The National Chemical Laboratory (NCL), Pune, an important research centre of the Council of Scientific and Industrial Research (CSIR), India, was 50 years old on 3rd January 1999. As part of the celebrations of its Golden Jubilee Year, an international conference on catalysis was organized at NCL during January 19–21. This is the first of a series of conferences to be conducted during 1999 in the various disciplines of research at NCL. The aim of the conference was to bring together scientists from different countries working in different areas of catalysis to enable the exchange of ideas and thoughts on some of the recent developments in catalysis research.

A total of 35 speakers delivered lectures covering a broad spectrum of catalysis research. The speakers (besides the 15 from India) were from 11 countries covering Europe, Asia and the Americas. There were a total of 8 technical sessions, each dedicated to a specific area in catalysis (*viz.*, catalytic reaction engineering, catalysis by micro and mesoporous materials, polymer catalysis, oxidation catalysts, homogeneous catalysis, chiral reactions over solid catalysts, modelling and simulation in catalysis and environmental catalysis) besides the inaugural and concluding sessions.

The inaugural address by Professor B. Delmon (Université Catholique de Louvain) recalled the innovations in catalysis brought out by environmental concerns, such as the development of monolith catalysts, auto exhaust converters and innovative and green processes for the production of chemicals. He was optimistic about the future of catalysis and spoke about the importance of new emerging concepts such as molecular recognition, spill-over phenomenon, remote control of catalytic sites and dynamic processes during catalysis.

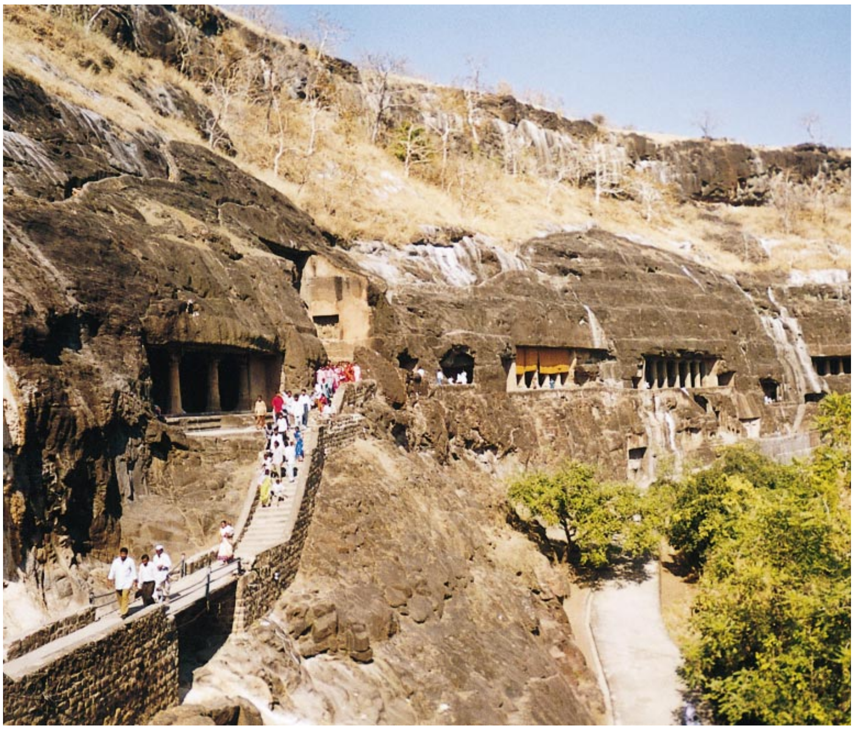
The first 'L.K. Doraiswamy Honor Lecture' was delivered by Professor James Wei, Dean of Engineering and Applied Science at Princeton University, in the session on catalytic reaction engineering intended to honour Professor L.K. Doraiswamy, Herbert L. Stiles Professor of Chemical Engineering at the Iowa State University, USA, and ex-director of NCL for his contributions in reaction engineering. In his lecture entitled 'Chemical Reaction Engineering at the Millennium', he charted the growth and decline of chemical reaction engineering as a discipline over the past few decades and projected for it a brighter future. Some of the notable speakers during the conference were Professor J. Haber (Poland), Dr. H-U. Blaser (Switzerland), Professor H. van. Bekkum (Holland), Professor U. Schuchardt (Brazil), Professor R. Catlow (UK), Dr. A. Miyamoto (Japan), Dr. P. Jenck (France), Professor F. Trifiro (Italy), Dr. Malli Rao (USA), Professor E. Kemnitz (Humboldt Univ., Germany), Professor B. Viswanathan (IIT, Madras), Dr. B. D. Kulkarni (NCL), Dr. P. Ganguly (NCL), S. Sivaram (NCL) and Dr. P. Ratnasamy (Director, NCL).

A notable aspect of this symposium was a session on environmental catalysis. In this session, Dr. Malli Rao (DuPont, Wilmington, USA) gave examples of steps including process innovations by the chemical industries in response to environmental concerns. The next speaker, Professor M.-F. Stephanopoulos (Tufts University) spoke on the activity of Ce-doped Ag-ZSM-5 as a catalyst for the catalytic reduction of NO_x with methane. Dr. V. R. Choudhary (NCL) presented his work on the coupling of endothermic steam reforming with exothermic oxidation of methane to achieve better control of the reaction.

Besides the papers presented in this session, a good number of papers dealt with different aspects of environmental catalysis and green chemistry. Dr. J. Jenck (Rhodia Polyamide Intermediates, France) presented a review of the recent trends in heterogenized homogeneous catalysts and pointed out how these catalysts fall short of the expectations of the chemical industry. Dr. H.-U. Blaser from Novartis Services AG, Basel, gave

Some of the catalysed reactions discussed at Pune

Reaction	Catalyst
Reduduction of NO_x with methane	Ce-doped Ag-ZSM-5
Hydroxylation of L-tyrosine to L-dopa	Cu acetate dimers encapsulated in zeolite
Selective oxidation of hydrocarbons	TS-1/Ti-beta
Synthesis of 4-*tert*-butylcyclohexanol	TS-1/Ti-beta
Hydrocarbon combustion	cubic ferrites

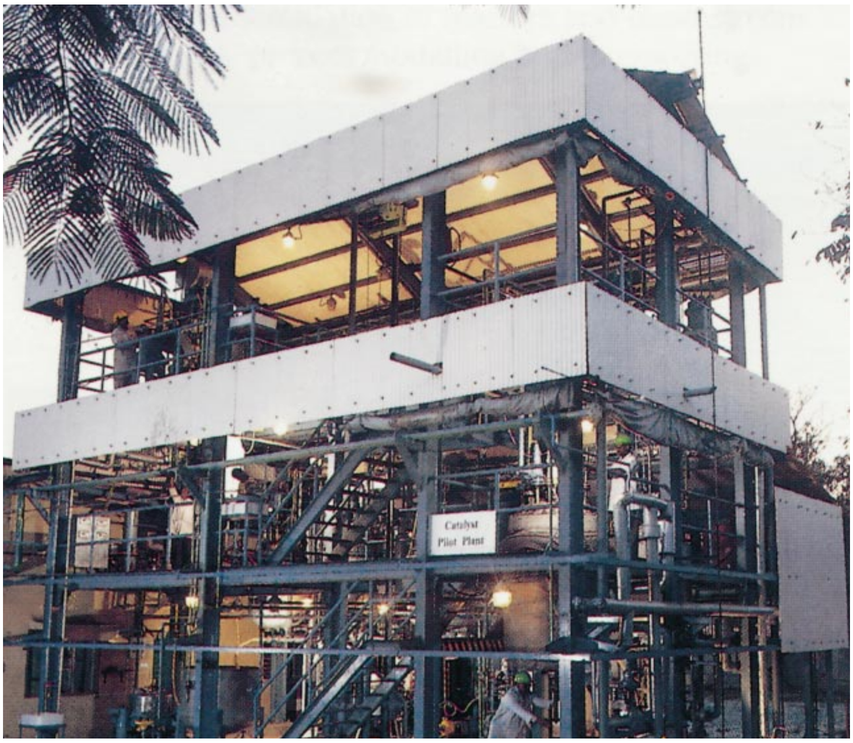


Delegates at the NCL Golden Jubilee Catalysis Conference visiting the Ajantha Caves.

examples of chiral heterogeneous catalysts used in the commercial synthesis of chiral compounds. Dr. M. K. Gurjar and Dr. Rajiv Kumar, both from NCL, spoke on their work using heterogeneous catalysts to prepare chiral and regioselective conversions of organic compounds. Dr. S. Sivasanker (NCL) spoke on the various features of micro- and meso-porous solid acid catalysts and how these have been beneficially used in developing novel green commercial petrochemical processes.

An emerging area where green catalysts are replacing homogeneous solution phase catalysts is in the selective oxidation of hydrocarbons. Professor F. Trifiro (University of Bologna, Italy) spoke on the requirements necessary for good heterogeneous selective oxidation catalysts for the oxyfunctionalization of alkanes. Dr. P. Ratnasamy, the Director of NCL and organizer of the symposium, showed how encapsulation of Cu-acetate dimers inside the alpha-cages of zeolite Y reduced the Cu–Cu distance (in the dimer) and enhanced its catalytic activity in the hydroxylation of L-tyrosine to L-dopa, a reaction typically catalysed by oxygenase enzymes. Dr. G. Bellussi of Eniricherche, explained how differences in the nature of the Ti species in TS-1 and Ti-beta are responsible for the differences in the activities of the two materials in selective oxidation reactions. Eniricherche has been involved in the development of green processes for the ammoximation of cyclohexanone, epoxidation of propylene and the hydroxylation of phenol using TS-1. Professor H. van Bekkum (Delft University of Technology, The Netherlands) described the stereoselective behaviour of Ti-beta and TS-1 in the synthesis of 4-*tert*-butylcyclohexanol. In the same session, there were two lectures on the use of cubic ferrites in the catalytic combustion of hydrocarbons; Dr. A.V. Ramaswamy (NCL) spoke on the Mn-ZrO_2 system and Professor E. Kemnitz (Humboldt University, Berlin, Germany) spoke on the Cr-ZrO_2 system. Professor Kemnitz spoke on the use of temperature programmed ^{18}O isotope exchange o study the mechanism of oxidation reactions. These stabilized ZrO_2 based oxidation catalysts are potentially useful in pollution abatement catalysis. Professor B. Viswanathan from the Indian Institute of Technology, Madras, presented a comparison of the activities of substituted heteropolyacids with some metallosilicates in selective oxidation reactions.

In between the sessions, during the lunch break of each day, poster papers (totalling about 30) authored by NCL researchers (mostly Ph.D. students) in catalysis were displayed. The participants evinced keen interest in the posters which covered all the major areas of catalysis research conducted at NCL. In the concluding session of the conference, Dr. S. Csicsery reviewed the activities during the eight technical sessions. After three days of intense scientific discussions, the participants were treated to an exposition of ancient Indian art at Ajantha and Ellora caves situated about 200 km from Pune.



The new catalysis pilot plant at the National Chemical Laboratory, Pune, which provides the ability to supply a few hundred kilograms of catalysts for commercial testing and production.

Environment and Profitability in the Israeli Chemical Industry

The Ministry of the Environment in Israel is running a series of conferences on ‘Environment and Profitability in the Chemical Industry’. The first of these on environmentally sound production processes and product design was held in Tel Aviv on March 15, 1999. The 1-day meeting was well attended by representatives from the Israeli chemical and allied industries. The opening remarks were made by the Chief Scientist at the Ministry of the Environment, Professor Uri Mingelgrin. The first session on Eco efficiency was opened by the guest speaker Professor James Clark from the University of York, UK, who described the growing importance of green chemistry in research, chemical manufacture and education. Other presentations in this session covered the criminal responsibility of employees and ISO14000. In the second session economic and environmental aspects of innovations in the treatment of water and air systems were considered. Presentations covered the use of bacteria and supercritical technologies in the treatment of industrial effluents, the chemical treatment of refrigeration systems without brine production, the use of solar systems in the chemical industry, ecotechnical plants for industrial effluent treatment and cleaning gas emissions. The third and final lecture session focused on implementations and included discussion of the fifth European framework programme, mapping and defining emissions from the chemical industry and applications for hydrogen peroxide in the chemical industry. The day finished with a panel discussion on the issue of cooperation between industry and the Ministry of the Environment to achieve common goals.

Tel Aviv—the venue for a conference on environmentally sound production processes and product design.

Herbert C. Brown Award for Creative Research in Synthetic Methodology

Another highlight of the 217th ACS Meeting was the presentation of the 2nd Herbert C. Brown Award to Professor Barry M. Trost of Stanford University, for his work in ‘Inventing Reactions for Atom Economy’. The award was presented to Professor Trost by the recipient of the first award, Professor Herbert C. Brown himself. Everyone in the enormous audience appreciated the massive contribution to organic chemistry made by the two recipients of the Award, which is sponsored by Aldrich Chemical Co. Inc. The presentation was followed by an excellent lecture by Professor Trost, which illustrated some of the work which had formed the basis of his contribution to the subject of atom economy. His overriding principle was that of using addition reactions of varying degrees of complexity to replace other, less atom efficient, routes. Many of these reactions were invented in the course of his work, and are based on organometallic catalytic reactions, often involving ruthenium complexes. The ability to have excellent chemoselectivity and avoid the use of protecting groups is another key feature of this chemistry, and the use of such principles in simplifying complex synthetic pathways was spectacularly illustrated by the reduction of a 30-step route to 6 steps.

Green Chemistry at Anaheim

Andrea Watson and John Rafelt (graduate students in the Green Chemistry Group at the University of York, UK) report from the ACS National Meeting

The 217th American Chemical Society National Meeting at Anaheim, California, from 21–25 March 1999 contained a one-day Green Chemistry Symposium within the Environmental Chemistry Programme. This symposium was organised by Tracy Williamson of the EPA and Joe Breen of the Green Chemistry Institute. The morning session consisted of presentations on technical advances, while the afternoon was concerned with educational issues.

Green chemistry technical session

Joe Breen opened the Green Chemistry program by thanking the audience for their attendance and stating that both the government and academia appreciated their interest. New publications and revised texts were given as evidence for the increasing awareness of green chemistry: specifically the birth of the RSC’s *Green Chemistry* journal and the inclusion of a chapter entitled ‘Aromatic Compounds in Green Chemistry’ in the 7th edition of Solomons organic textbook. As an example of green chemistry being incorporated into everyday life it was mentioned that the first dry cleaning shops to use liquid carbon dioxide as opposed to chlorinated solvents had opened in Boston and St. Louis. It also turned out that Breen’s own suit had been cleaned using this new environmentally friendly method.

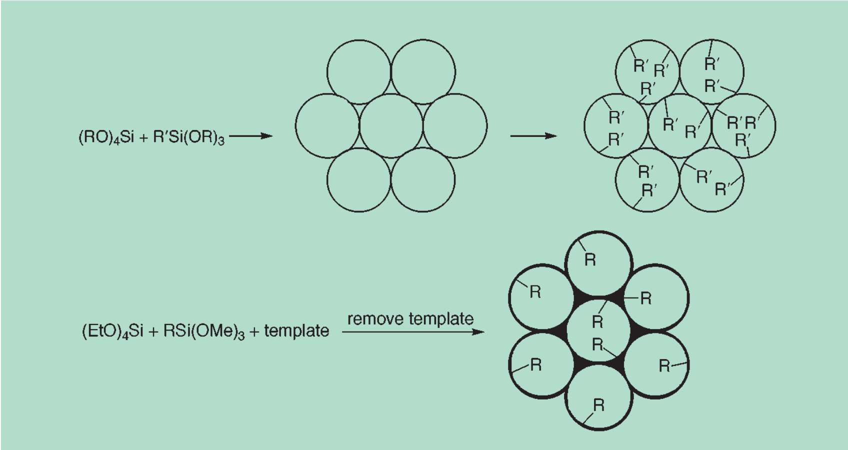
In the first lecture Rajender Varma (Sam Houston University, Huntsville, Texas) spoke of solventless syntheses using supported reagents and microwaves. Microwave irradiation of heterogeneous systems involving just the neat reactants in the presence of a solid mineral support has delivered significant rate enhancements. This is due to the presence of adsorbed organics on the solid surface which absorb microwaves causing localised heating. The advantages of using solid phase rather than solution phase chemistry are numerous:

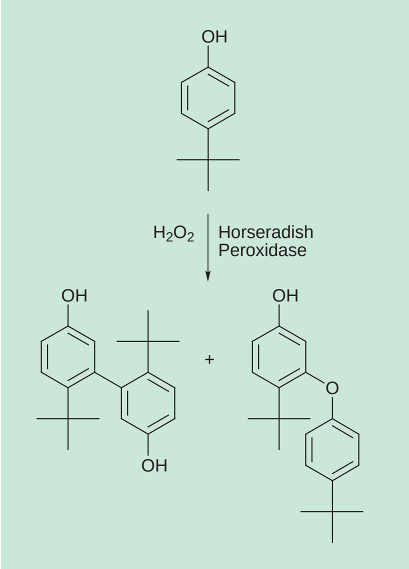
- Good dispersion of the active reagent results in an improvement of reactivity.
- The constraints of the pores and the characteristics of surface adsorption can result in a useful improvement in reaction selectivity.
- Solids are generally safer and easier to handle than liquids.
- Elimination of organic solvents prevents pollution at source,
- As both products and the support/ catalyst are recyclable the method is environmentally benign in nature.

Varma outlined an overwhelming number of organic syntheses carried out under solid phase conditions. The wide range of reactions covered (protections/deprotections, cyclizations, rearrangements, oxidations, reductions) all yielding high conversions and selectivities gave a feel for the extent of activity and success already achieved in this field.

In the second lecture, Duncan Macquarrie (University of York, UK) spoke about the use of chemically modified silicas as catalysts for green chemistry. Two preparation procedures were outlined (see top box), one being a two-step grafting synthesis and the other a one-pot sol–gel procedure using a micelle template. The properties of the materials were related to the criteria necessary for an ideal catalyst and the application of the most promising materials in organic syntheses was discussed. An ideal catalyst would have a high surface area with well-defined pores, be robust and have flexibility overloading and surface polarity. Materials prepared by the templating method make particularly attractive catalysts. Pore sizes are well-defined and tuneable, stability is good and loadings, which may be easily varied, may be as high as 4.85 mmol g^{-1} (at least 5 times higher than that achieved previously). A bifunctional phenyl/aminopropyl hexagonal mesoporous silica was reported to be a particularly highly active base catalyst for the Michael and Knoevenagel reactions.

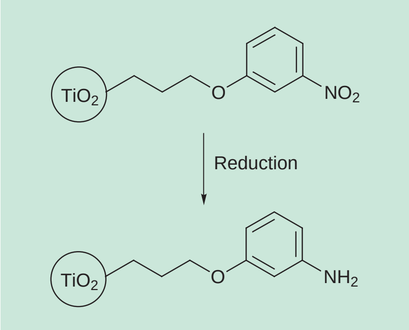
In the third lecture, Bruno Rindone (University of Milan, Italy) outlined the use of the enzyme horseradish peroxidase (HRP) as a catalyst for bimolecular coupling reactions of phenoxyl radicals. Although the active component of the enzyme is the iron metal centre, it is encapsulated within a protein and so presents no environmental threat. Organic compounds obtained from such reactions have an important biological role: they constitute organic polymers such as lignin, lignans, suberin and algal cell wall. The problem with many bimolecular phenoxyl radical coupling reactions is that contrary to biological oxidation they do not proceed under strict regio- and stereospecific control. However, in his presentation Rindone reported that enantioselective oxidative phenol coupling of a ferulic acid amide had been achieved using HRP as catalyst and the ethyl (*S*)-alaninate group as chiral auxiliary.





The second session was opened with the second presentation of the morning from Rindone. Entitled ‘Green Oxidations’, the merits of functionalising unactivated carbon–hydrogen bonds was discussed. With the majority of the work concerning the use of ozone, applications including the preparation of amides from amines, the oxidation of cyclodecane and the oxidation of decalins supported the use of this oxidant for environmentally friendly synthesis. Highlighting another area of clean synthesis, Gunilla Jacobson (Los Alamos National Labs) gave an informative review of biphasic catalysis with particular reference to the use of water/carbon dioxide micellar systems. The main advantage of this supercritical system is that it allows easy phase separation of products by a reduction in temperature and pressure. Using a homogeneous ruthenium catalyst with an organo-phosphorus salt, the oxidation of higher olefins to aldehydes was shown to be greatly enhanced using this method.

The last presentation of the session was given by Partch of Clarkson University, NY, concerning the synthesis of heterocycles *via* reactions on photo semiconductor surfaces. The external functionalisation of titania particles with alkyl functions terminating in nitro aromatic groups was explained, and electrolysis of this species was shown to cause reduction of the nitro functions to aniline functions. This technique represents a useful tool for surface modification without the use of heavy metals and hydrogen.



An interesting and informative morning highlighting the variety of areas in which old traditional chemical methods are being carried out more efficiently utilising methods which produce little waste and high conversion.

Educational presentations

The first talk of the afternoon session was given by Joe Breen, and was entitled 'ACS/EPA Green Chemistry Educational Outreach Project'. This project involves about 30 academics and industrialists, who are working to generate educational material for the undergraduate and graduate levels. The project was initiated at a planning conference in Washington, DC, in October 1998. The aims of the project team include the development of curriculum material to be incorporated in 'Chemistry in Context' and 'ChemCom', two very popular chemistry textbooks. Material for popular chemistry magazines will also be developed and promoted. Drop-in modules for existing courses are also planned, and will include laboratory material as well as case studies (discussed in more detail by Mike Cann–see below). Professional Development short courses in Industrial Ecology and Green Chemistry are also under development. Dissemination of the activities of the project is planned through brochures, newsletters, conferences, and presentations at conferences and in lecture tours.

The next speaker, Conrad Stanitski (University of Central Arkansas) is the author of 'Chemistry in Context'. His presentation was centred on the theme of green chemistry being a vehicle for improving the image of chemistry by putting various events into a historical perspective. By doing this one can show how chemistry can improve quality of life and solve the problems which can arise along the way. 'Chemistry in Context' is written for non-science majors (who must still take one science option) and uses issues to introduce the chemistry. His ideas for integrating green chemistry into 'Chemistry in Context' include the use of the Presidential Awards as a source of material for Web-based exercises, and by the addition of halon substitutes such as Pyrocool (itself a Presidential award winner) and water and carbon dioxide-based cleaning systems into existing chapters. Synthetic chemistry, such as the classic BHC ibuprofen synthesis would also make an excellent example.

Stanley Manahan (University of Missouri) gave a talk on green chemistry in the context of general environmental chemistry. He discussed the overall transformations which take place in all parts of the environment, and how events in one part can influence those in other, apparently separate, parts. The importance of understanding the whole, rather than just individual parts was discussed. The chemistry of the ozone layer and its effects on the whole planet's chemical and biochemical processes was put forward as an excellent example of this, and of how environmental chemistry can identify and solve problems. The development of CFCs as excellent refrigerants, which turn out to have serious drawbacks, and the subsequent elucidation of their atmospheric chemistry, followed by the production of improved replacements is a dramatic example of how an overview of processes in all parts of the planet can be used to put forward intelligent measures in a reasonable timeframe.

John Warner of UMASS gave a very lively talk on green chemistry in an undergraduate setting, in particular non-science majors. The major issues he identified here were the opinions of non-scientists of science, the difficulties in communicating the many benefits and excitement of science, and the perception of industry. Again, green chemistry can be used as an ideal vehicle for the communication of good news from chemistry, as it relates to the improvement of many products and processes which everyone experiences in daily life. Their perception of the positive role of chemistry is thus enhanced, and the efforts to minimise the negative aspects are simultaneously explored. As an ex-industrialist, he also discussed the need for industry to incorporate more and more green chemistry into R&D. The scale-up process is often when potential environmental difficulties first become apparent, but this is often too late to solve them effectively (for a further discussion of this topic, see the article by Jim Bashkin in Issue 2 of *Green Chemistry*). The incorporation of green chemistry into the earliest stages of a products life will help industry, government and academia, the latter through a richer source of case studies. John also gave details of an annotated bibliography on green chemistry which he is currently producing.

The use of the Presidential Green Chemistry Awards as a source of project material was introduced by Mike Cann (University of Scranton). In an excellent presentation, Mike gave a thorough account of an exercise developed by him, which uses Presidential Award winners' proposals as a source of information. Groups of students each choose one of the Award projects as the basis for a poster presentation. The students work through the proposals and identify both the problem and the solution arrived at by the proposer. This makes them define the real nature of the green chemistry involved and the approach taken by the award winner. The students have to gather extra information from the Web and must also contact the award winner to discuss the chemistry. This poster event is run in the Environmental Chemistry Section of a Chemistry/Biology course, and lasts one semester.

The final talk of the session was given by Ralph Taylor-Smith of Lucent Technologies. He introduced the audience to the work of the Lucent Foundation. This foundation was set up to fund projects in the area of Industrial Ecology, environmental issues and awards grants annually to fund projects in environmental research. These grants are available to anyone, and currently around a quarter of the 60–70 proposals (most, but not all, from the US) receive funding. Typical project duration is 2 years, and the projects are split, roughly 50:50, between physical science /engineering and policy / management / law. Academic partners are provided with an industrial mentor to facilitate technology transfer.

Green chemistry discussed at Anaheim

- **Solid-phase reactions**
- **Microwaves in synthesis**
- **Modified silicas as catalysts**
- **Bimolecular phenoxyl radical coupling reactions**
- **Green oxidations**
- **Biphasic catalysis**
- **Atom economy**
- **Heterocyclic synthesis *via* reactions on photo semiconductor surfaces**

Green chemistry resources recommended at Anaheim

- ***Green Chemistry* journal (RSC)**
- **'Aromatic Compounds in Green Chemistry' in the 7th edition of Solomons organic textbook**
- **ACS/EPA Green Chemistry Educational Outreach Project materials**
- **'Chemistry in Context' by Conrad Stanitski (University of Central Arkansas)**

The foundation has recently been joined in this work by the National Science Foundation (http://www.nsf.gov/). Ralph's parting comments were that the real challenge, from his viewpoint, was converting the principles of green chemistry to industrial manufacturing practice.

Optimisation of Environmental Properties in the Development of New Chemical Products

In recognition of the increasing importance to consider environmental issues during the synthesis, application and disposal of new chemical products a 1-day seminar to address these problems was organised by the LGC in conjunction with Peter Fisk Associates. This meeting, held on 30th March 1999 at the University of Greenwich, UK, attracted over 50 delegates from industry and academia. Lecturers with experience in regulatory affairs, bio-organic chemistry, ecotoxicology, green chemistry and the chemical industry were invited to give their views on the problems that must be considered if the environmental impact of new chemicals is to be improved.

Early consideration of green issues

The introduction by the chairman Professor Tony Beezer, of the University of Kent, set the scene for the day by outlining how current approaches to new chemical synthesis, where consideration of regulatory affairs is only made at a late stage of development, must change. This view was given further support by Elizabeth Surkovic, of the Chemicals Industry Association, and Dr Steve Robertson of the Environment Agency. Both stressed the importance for industry to assess the safety of new products at an early stage of development and reconsider the use of particularly hazardous preparations, avoid the formation of toxic side-products and minimise undesirable properties of the new product. Overall the opinion was that the profile of the chemical industry is dependent on a more cautious and responsible approach being adopted towards the risks posed to the environment by the use of hazardous chemicals.

Biodegradability, bioaccumulation and ecotoxicology

The next session of the meeting addressed ways in which these factors should be considered in designing environmentally friendly chemicals. Dr Gary Robinson, Lecturer in Environmental Biotechnology at Kent University, discussed the role of microorganisms in chemical biotransformation and biodegradation, stressing the importance of maintaining enzyme–molecule compatibility when adding functional groups to biodegradable compounds Methods for assessing the bioaccumulation of potentially toxic compounds were then discussed by Dr Peter Fisk. Bioaccumulation encompasses 3 main themes, the concentration of the toxic compound between water and the microorganism, the accumulation of the compound in the organism, and the subsequent uptake of the toxic compound in the food chain. In practice, measurement of bioaccumulation is expensive, requiring field tests, so predictive models based on the use of the octanol–water partition coefficient are preferred in the initial stages of assessment. Expanding this theme to the assessment of ecotoxicology, Dr Andrew Girling, a consultant ecotoxicologist, discussed the consequences of introducing toxic chemicals into the environment and methods that are being developed to allow all chemical manufacturers, large and small, to test the toxicity of their new compounds. Recent developments include the availability of ECO test kits, which allow laboratories to grow small cultures of organisms including Daphnia (water flea) and fish eggs to test the effect of their new chemicals. Overall it was emphasised that the use of these tests at an early stage of a project would be more cost effective than having long running projects aborted at the final assessment stage of the product.

Implementing chemical assessment

Dr John Mitchell and Professor Dick Hyde of the University of Kent combined their respective research experiences in bio-organic chemistry and the pharmaceutical industry, in the afternoon session to discuss new tools available for chemical assessment. They explained how advances in drug discovery technology such as high throughput screening methods should allow databases of molecular properties to be compiled, and enable the assessment of environmental acceptability of suitable chemicals at very early stages of the project.

Think green!

The importance of re-education of chemists to think 'Green' was then stressed by Professor James Clark of the University of York Clean Technology Centre, who explained how the poor image of the chemical industry can have a detrimental effect on the popularity of chemistry at an undergraduate level. He described the aims of the RSC Green Chemistry Network, which hopes to promote awareness of the practice of green chemistry in industry, academia and schools, through considering waste prevention rather than removal. Two case histories where such an approach has been successful were then presented by Dr Roger Van Egmond of Unilever, and Dr Nigel Battersby of Shell, who discussed their respective experiences in the development of biodegradable cationic surfactants and hydraulic fluids. The meeting was concluded by Dr Peter Fisk, who suggested some approaches that could be adopted by laboratory management to implement the ideas presented during the meeting.

Karen Wilson, University of York

ET'99

ET'99 which runs at the NEC Birmingham, UK, from June 8–10, 1999, will include a 3-day seminar with the following six themes:

- Understanding the implications of the integrated pollution prevention control (IPC) directive
- The practicalities of working with the environmental impact assessment (EIA) directive
- Water: successfully managing resources
- Successfully meeting the challenges of waste management
- Effectively managing and remediating contaminated land
- Using performance indicators, environmental benchmarking and performance management systems to improve your company's environmental accountability

The speakers will include representatives from the Environment Agency, DETR, The Institute for Environmental Assessment, AEA Technology Environment and the Environmental Services Association.

Further information on the event can be obtained from IBC UK Conferences Ltd (Tel +44 (0)171 637 4383; Fax +44 (0)171 631 3214).

Conference Diary

JULY 1999

Gordon Research Conference on Green Chemistry — **July 11–16**
Queen's College, Oxford, UK
(http://www.grc.uri.edu/programs/1999/green.htm)

Advances in Polymerisation Methods Controlled Synthesis of Functional Polymers — **July 12–15**
Institute of Macromolecular Chemistry, Prague, Czech Republic
(sympo@imc.cas.cz)

Pre-OMCOS Symposium on Organometallics and Catalysis — **July 15–16**
Rennes, France
(http://www.univ-rennes1.fr/umr6509/pre-OMCOS)

10th IUPAC Symposium on Organometallic Chemistry Directed towards Organic Synthesis — **July 18–22**
Versailles, France
(genet@ext.jussieu.fr)

7th International Symposium: The Activation of Dioxygen and Homogeneous Catalytic Oxidation-ADHOC99 — **July 19–23**
University of York, UK
(http://www.rsc.org/lap/confs/adhoc-99.htm)

AUGUST 1999

218th American Chemical Society National Meeting, with Symposium on Green Chemistry: Chemicals and Materials from Renewable Resources — **August 22**
New Orleans, USA
(natlmtgs@acs.org)

SEPTEMBER 1999

4th European Congress on Catalysis (Europacat 4): Catalysis and Chemical Technologies for a Sustainable Future — **September 5–10**
Pala Congressi, Rimini, Italy
(http://www.fci.unibo.it/ec4)

The 2nd Post-Graduate Summer School on Green Chemistry — **September 6–12**
Venice, Italy.
(http://hydra.unive.it/inca/summer/index2.htm)

Biotrans '99 — **September 26–October 1**
Giardini Naxos-Taormini, Sicily, Italy
(http://dept.chem.polimi.it/biotrans)

OCTOBER 1999

Catalysis Technology Car Boot Sale — **October 7**
Weston Building, Manchester Conference Centre, Manchester, UK
(http://www.chemsoc.org/bootsales/home.htm)

3rd European Biofuels Forum — **October 11–13**
Palais des Congres, Brussels, Belgium

NOVEMBER 1999

GRIF'99 (Gateway to Renewable Industrial Feedstocks) — **November 2–3**
John Innes Centre, Norwich, UK
(http://www.actin.co.uk)

Environment China '99 — **November 2–5**
Guangzhou, China
(environment@gima.de)

International Congress of Chemistry and Environment — **November 27–30**
Indore, India
(http://www.chemenviron.com)

January 2000

2nd Asia-Pacific Congress on Catalysis — **January 31–February 2**
Sydney, Australia
(http://www.chemsoc.org/events/_events/00001018.htm)

APRIL 2000

CAPoC5–5th International Congress on Catalysis and Automotive Pollution Control — **April 12–14**
Universite Libre de Bruxelles, Belgium
(http://www.ulb.ac.be/sciences/surfcat/CAPoC5/)

MAY 2000

16th Canadian Symposium on Catalysis — **May 23–26**
Banff, Alberta, Canada
(http://www.gch.ulaval.ca/~sayari/16csc/)

Green chemistry

The sonochemical approach

Pedro Cintas*[a] **and Jean-Louis Luche***[b]

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Received 21st January 1999

Summary

Although the applications of ultrasound have long been known in both industry and academy, the “green” value of the non-hazardous acoustic radiation has been recognised by synthetic and environmental chemists only recently. The chemical and physical effects of ultrasound arise from the cavitational collapse which produce extreme conditions locally and thus induce the formation of chemical species not easily attained under conventional conditions, driving a particular radical reactivity. This rationale, accessible in a non-mathematical manner, anticipates the advantages of using this technology in a variety of processes that include milder reactions with improved yields and selectivities, easy generation of reactive species and catalysts or replacement of hazardous reagents. Sonication enables the rapid dispersion of solids, decomposition of organics including biological components, as well as the formation of porous materials and nanostructures. This review summarises how ultrasound can be harnessed to develop an alternative and mild chemistry, which parallels the ability of acoustic waves to induce homolytic bond cleavage.

Introduction

The popularization of ultrasound in life and society is linked to its widespread usage in medicine.[1] Most recently, there have been impressive developments in the field of chemical synthesis,[2,3] including materials science, aerogels, food chemistry, and other research areas assisted by ultrasound.[4] Recent and innovative applications illustrating the mildness and non-hazardous character of these waves relate to their potential in Green Chemistry. The role of sonochemistry in the creation of ‘benign-by-design’ synthetic methods is clear from the definition of this expression: low level of waste, inherently safe, material- and energy-saving, with an optimised use of non-renewable resources, and a preferential exploitation of renewable ones. Green Chemistry is already an important topic in academic and industrial research, because it ‘. . .challenges us to create new ways to more efficiently produce useful products with less waste, or preferably no waste’.[5] Sonochemistry corresponds to these objectives, since some of its main advantages are:

(a) the possibility to change the course of a reaction to reach new selectivities *via* sonochemical switching (see below for definition)

(b) the improvement of rates (energy savings), yields, and selectivities (reduced wastes)

(c) the possibility to use non-classical reagents or reagents obtained under unusual conditions, even aqueous media (safety, energy savings).

Examples of these advantages are described in this paper, and more complete literature coverage can be found in previous publications.[2–4] In the future, compatibility with other physical methods, *e.g.* microwaves plus ultrasound, or light plus ultrasound,[6] which is just starting to be explored, should enlarge considerably the range of applications.

Sonochemistry: how it began

The first report of the influence of ultrasound on chemical reactions appeared 70 years ago,[7] but applications did not follow, due to technical reasons essentially. Subsequent work demonstrated the mechanical (cleaning, disruption of solids, *etc.*) and chemical effects (formation of free radicals) of ultrasound, the latter evidencing some similarities between sonochemistry and radiochemistry.[8] The cavitational implosion produces radicals from most solvents, which in the case of water are the $H^\bullet$ and $OH^\bullet$ species (Scheme 1).[9]

$$\begin{array}{lcll}
H_2O & \longrightarrow & H^\bullet + HO^\bullet & (1)\\
2\ HO^\bullet & \longrightarrow & H_2O_2 & (2)\\
2\ HO^\bullet + 3\ I^- & \longrightarrow & 2\ HO^- + I_3^- & (3)\\
O_2 & \longrightarrow & 2\ O^\bullet & (4)\\
2\ HO^\bullet & \longrightarrow & H_2O + O^\bullet & (5)\\
2\ O^\bullet & \longrightarrow & O_2 & (6)
\end{array}$$

Scheme 1 Water sonolysis and a few subsequent reactions.

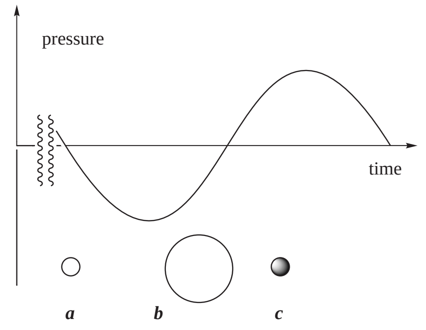
Green Context

The use of ultrasound as a means of accelerating reactions is an important technique and one which is rapidly developing. The ability to efficiently deliver energy to a system in such a way that solvent is not required, and the observation that selectivity can be very high makes sonochemistry a technique of some potential in green chemistry. This review article gives an accessible account of the technique, and the observation that includes theoretical background as well as applications to organic synthesis, and to the preparation of heterogeneous catalysts of novel morphology. For other potentially green techniques see Green Chemistry issue 1 p. 43 (microwaves) and for heterogeneous catalysis see issue 1 pp. 1, 33, 35 and issue 2 pp. 69, 75, 83. ***DJM***

These radicals can recombine or react with other substances to induce secondary reduction and oxidation reactions. For example, iodide is sonochemically oxidised to triiodide by $OH^{\bullet}$ radicals [eqn. (3)], a reaction used for dosimetry.[10] Aqueous solutions containing chlorocarbons (*e.g.* CCl_4), liberate $Cl^{\bullet}$ and Cl_2 in high yields, and molecular oxygen if present is decomposed [eqn. (4)].[11] Examples of a frequency effect have been found: for instance, the yield of hydrogen peroxide, from the recombination of $OH^{\bullet}$ radicals, is higher at 514 kHz than at 20 kHz.[12] The high energies involved in these processes are illustrated by the fixation of atmospheric nitrogen as nitrous and nitric acids by sonication at 540 kHz of air-saturated water.[13] Hydrogen cyanide, formaldehyde, imidazole and amino acids, for example, are formed from sonicated aqueous solutions of nitrogen, hydrogen, carbon monoxide and methane,[14] this is sometimes suggested to be relevant to prebiotic chemistry. Of more immediate interest, studies are in progress on the effects of sound waves on biomolecules and polymers in aqueous media,[15,16] a model for biological fluids and tissues.[1] Concerning applications in organic synthesis, the preparation of organometallics in undried solvents from unactivated metals was reported by Renaud in 1950.[17] Thirty years later, the facile sonochemical formation of organolithium and Grignard reagents and the Barbier-type coupling with carbonyls was described.[18] This result, along with the reductive dehalogenation of dibromoketones with ultrasonically dispersed mercury,[19] represents the jumping-off point of modern sonochemistry.

Cavitation, the basic phenomenon in sonochemistry

In contrast to electromagnetic radiation, acoustic waves are not able to alter electronic, vibrational, or rotational molecular states. The resulting chemical effects must therefore originate from a relay phenomenon, cavitation. An acoustic wave is a pressure wave made of alternate compressions and rarefactions able to break the intermolecular van der Waals forces maintaining the cohesion of the liquid (Scheme 2). Gas-filled microbubbles start growing especially in the vicinity of inhomogeneities (tiny gas bubbles, solid impurities, *a* in Scheme 2) to reach state *b*.[20] Under the action of the destabilising Laplace forces, these bubbles collapse to *c* in *ca*. 1/5 of a cycle or less, *i.e.* $<10^{-5}$ s for a frequency of 20 kHz, or 4×10^{-7} s at 500 kHz.

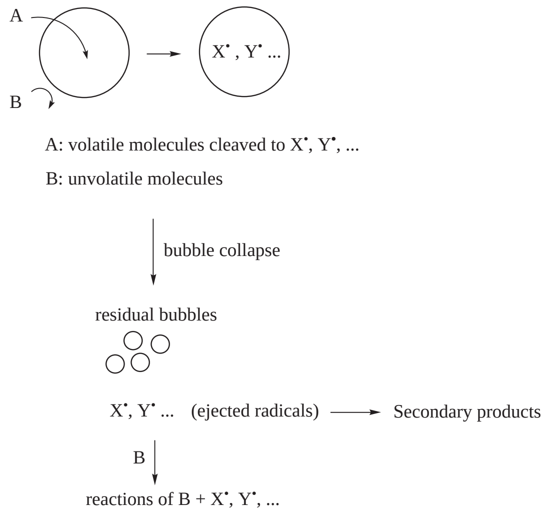


Scheme 2 Dynamics of cavitation bubbles.

The collapse is accompanied by the emission of light flashes in the 200–700 nm window.[21] This sonoluminescence, which occurs for both aqueous[22] and non-aqueous liquids,[23] constitutes a means to determine which are the actual physical conditions inside the bubble.

Theoretical interpretations of cavitation

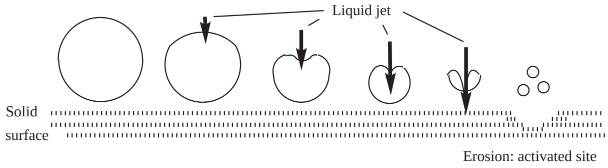
Two different theories are currently used to explain sonochemistry and sonoluminescence. In the thermal ("hot spot") theory, temperatures estimated at ≈5000 K[24] and pressures of ≈1700 bar are produced during the collapse.[25] Sonoluminescence studies provide numerical estimates of duration (<100 ns) and cooling rates $>10^{10}$ K s^{-1}.[26] Accordingly, this nearly adiabatic process releases sufficient energy to generate then stabilise highly reactive species by thermal quenching. However, calculations based on the laws of classical thermodynamics may be invalid due to the highly out−of−equilibrium character of the phenomena, and large variations are recorded in the temperature estimations. Recent findings suggest temperatures ranging from 5000 to ≈20 000 K, or higher.[27–31] Nevertheless, this picture provides an intuitive rationale for understanding how sonochemical reactions occur (Scheme 3): volatile molecules penetrate the bubbles and the conditions produced during the collapse are sufficient to break bonds homolytically. The collapse sends the radicals into the bulk liquid where they react at room temperature.



Scheme 3 Topology of reactions in a bubble field.

Obviously, this chemistry should depend on the relative lifetimes of the radicals thus produced and of the bubbles, but frequency effects[12] are not taken into account in most synthetic studies. Substances of low vapor pressure, which are unable to penetrate a bubble, still experience a high energy environment from the shock waves associated with the bubble collapse, or react with the radical species generated by the sonolysis of any volatile compound present in the medium, such as the solvent. However, the alternative electrical theory claims that lower temperatures and pressures are involved but electrical discharges accompany the collapse.[32] This theory, based on a double-layer model, has been the subject of numerous criticisms,[33] essentially because in sonicated water the hydrated electron (e_{aq}^{-}, or $H_2O^{-\bullet}$),[34] which should form under such conditions, can not be detected unambiguously.[35]

The sonochemical activation in heterogeneous systems is mainly a consequence of the mechanical effects of cavitation:[36] a liquid jet propagates towards the phase boundary at a velocity of several hundred meters per second, and hits the surface violently (Scheme 4). At a liquid–liquid interface, the mutual injection of



Scheme 4 Cavitational erosion of solids.

droplets results in emulsification. On a solid, the intense physical stresses produce particle breakage, the importance of which depends, *inter alia*, on the lattice energy of the solid.[3*b*,37] In addition, cavitation greatly accelerates mass transport,[38] and repassivation by reaction products is made less important or even avoided.[39]

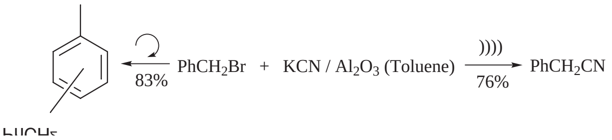
For practitioners, the physical considerations above may seem irrelevant, but factors affecting cavitation such as the nature of solvents or the volatility of substrates are certainly of crucial importance for understanding how such high energy chemistry can be performed in a simple flask.[40] Consequently, solvent effects in sonochemistry should not be calculated in terms of the common parameters such as Brønsted and Lewis acidity and basicity, dipole moments, *etc.*, but rather the volatility, viscosity or surface tension directly involved in the bubble formation and dynamics, and their ability to generate radicals, should be taken into account.

Besides *acoustic* cavitation, recent studies have also highlighted the importance of *hydrodynamic* cavitation created by the turbulent flow of liquids.[41] The chemical effects of both types of cavitation can be identically correlated with experimental parameters such as the bulk temperature and the nature of the dissolved gas.

Characteristics of sonochemical reactions

Analysis of numerous experiments shows that ultrasound has no significant or specific effect on many chemical pathways. Thus, in heterogeneous reactions, sonication has the same effects of rate and yield enhancements as high-speed stirring, due to mechanical effects. The chemical effects of ultrasound ('true sonochemistry') can occur only if an elemental process of the reaction examined is sonication sensitive or when a high energy species released by the collapse does participate as an intermediate. In this context, one speaks appropriately of ultrasonic activation and sonocatalysis, revealed by changes in product distribution, mechanism switching, and in some instances alterations of regio- and diastereoselectivity.[42]

The term 'sonochemical switching' was coined by Ando *et al.*,[43] who observed that sonication can change the nature of the products formed in a reaction, as exemplified in Scheme 5.



Scheme 5 The first sonochemical switching.

Ultrasound favours the substitution mechanism at the expense of Friedel–Crafts alkylation which is preferred under mechanical agitation.

After this first example other cases were reported, in which sonication induces a specific reactivity under both homogeneous[44] and heterogeneous conditions.[45] Since purely mechanical effects cannot explain such qualitative changes, cavitation must have direct chemical consequences. Accordingly, a set of empirical rules provides clues for future work and permits the distinction between true and false sonochemistry.[46]

Type I: Sonication of solutions favours sequential electron transfer (ET) and the formation of radicals.[47] Transition metal complexes undergo ligand–metal bond cleavage giving coordinatively unsaturated species. In contrast, homogeneous ionic reactions should not be affected by sonication.

Type II: In heterogeneous liquid–liquid or liquid–solid polar reactions, the mechanical effects of cavitation can affect both rates and yields to an extent depending on the characteristics of the system, such as the surface tension, density, temperature or nature of the phases. These are in fact cases of false sonochemistry.

Type III: In heterogeneous reactions following either an ionic or an ET pathway, sonication induces the latter preferentially. Biphasic systems are also subjected to mechanical activation in addition to chemical activation. In reactions involving metals, the sonochemical effects are usually attributed to 'cleaning' or surface depassivation, but some results support the idea that sonication makes electron transfer from the metal easier.[48]

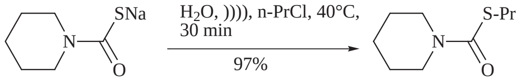
Sonochemical methods applied to green chemistry

Rate and yield improvements

Diverse types of reactions (substitutions, additions, reductions, *etc.*) are improved in terms of rates and yields by sonication. The *a posteriori* interpretation shows that some of these correspond to a chemical activation process, while a number should be ranked among the cases of false sonochemistry for which only mechanical effects are involved.

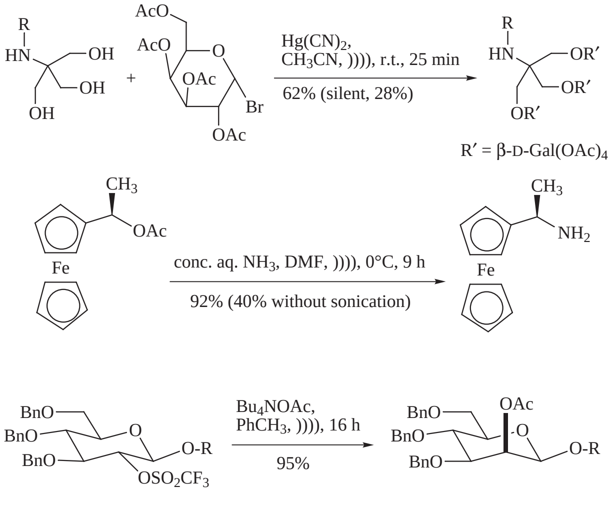
Substitution reactions

A good illustration is provided by the preparation of thiocarbamates (Scheme 6), for which a direct comparison is given between the sonochemical reaction and its analogues run under hydrodynamic cavitation and conventional stirring. The rate constants are in the relative ratios of 10, 12 and 1 respectively for the three methods.[49] Cavitational activation improves the yields, probably because the rate increase occurring even at ambient temperatures avoids decomposition of the thermally sensitive compounds.



Scheme 6 Synthesis of thiocarbamates.

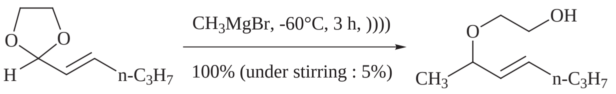
A few other examples are shown in Scheme 7. Clean and fast substitution by an alkoxy group occurs at the anomeric position on a bromo-sugar. The reaction is stereoselective: only the β-anomers are obtained,[50] while the conventional method gives mixtures.



Scheme 7 Examples of substitution reactions.

In 1-ferrocenylethyl acetate, substitution of the ester group by the amine functionality is achieved in yields up to 92% under sonication, without disturbance of the organometallic moiety.[51] Similarly, the triflate group in a sugar derivative precursor to Caloporiside is smoothly displaced by an acetate when sonicated in the presence of tetrabutylammonium acetate in toluene. The yield is quantitative and no undesired stereoisomer is formed.[52]

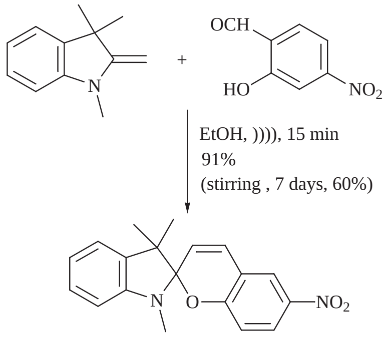
Grignard reagents react with α,β-unsaturated dioxolanes at −60 °C in the presence of ultrasound (Scheme 8).[53] Synthetically valuable yields are obtained, even at low temperatures and in the absence of Lewis acid catalysts. With stirring only, very low yields are observed. If a S_N2' *vs.* S_N2 competition exists, the relative yields are not changed by sonication.



Scheme 8 Reaction of Grignard reagents with unsaturated dioxolanes.

Additions

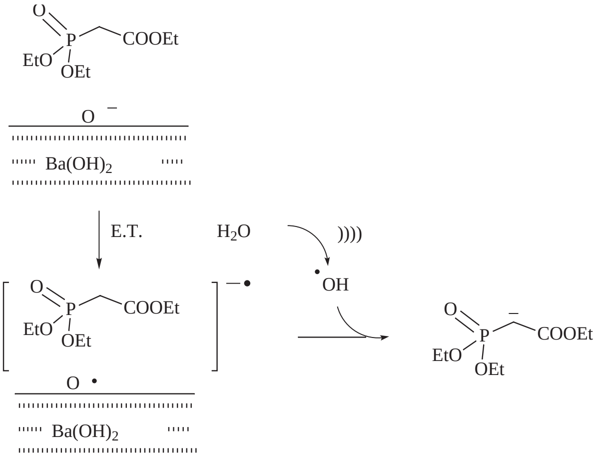
The preparation of photochromic spiropyrans by condensation of salicylaldehyde and a methyleneindole undergoes a spectacular rate increase when sonicated (Scheme 9).[54] A practically quantitative yield is obtained in a few minutes, instead of several days conventionally.



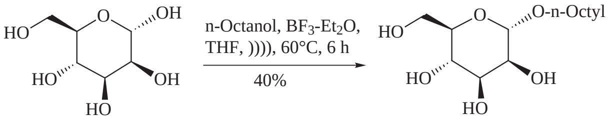
Scheme 9 Preparation of spiropyrans.

Sonication of Wittig and related reaction systems improves their synthetic potential,[55,56] even with enolisable aromatic ketones.[57] Instead of the usual strong and expensive bases requiring anhydrous media, alkali carbonates or hydrogencarbonates can be used.[58] The Wittig–Horner reaction on barium hydroxide represents a model case giving evidence of the chemical effects of ultrasound (Scheme 10):[59] sonication cleaves the water molecules present in small amounts (yields are much lower in dry solvents) to hydroxyl radicals which give the carbanion from the phosphonate radical anion generated on the catalyst surface.

Reactions starting from sugars constitute an important domain for the development of organic syntheses from renewable natural resources. In heterogeneous mixtures, the mechanical role of ultrasonic waves accelerates the acid-catalysed acetalisation of sugars,[60] in a clean and high-yielding reaction. From unprotected sugars, acetalisation with long chain aldehydes (from hexanal to undecanal) and perfluoroalkanals,[61] and glycosylation with long chain alcohols (Scheme 11) was effected by this method.[62,63] These reactions constitute a direct access to new sugar-based amphiphilic compounds.



Scheme 10 Wittig–Horner reaction catalysed by barium hydroxide.



Scheme 11 Glycosylation of unprotected sugars.

Easy generation of reactive species

Since the extreme conditions generated by the cavitational collapse lead to the homolytic cleavage of volatile molecules, attempts were made to use the resulting radicals for synthetic purposes. However, most homolyses proceed in low yields, and successful uses of the chemical effects of sonication are to be expected for chain reactions essentially. On the other hand, useful reagents prepared by difficult, long or expensive methods can be made readily accessible by sonochemical methods. Both types of reactions are illustrated in this section.

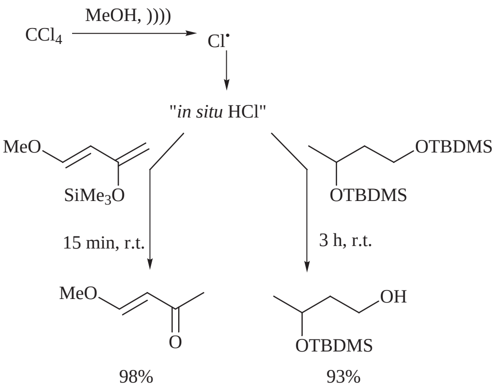
Formation of radicals

The sonolysis of water yields the hydroxyl radical and hydrogen atoms.[9] Similarly, sonication of organic solvents also leads to homolysis, and the species formed in the largest amount is the hydrogen atom.[64] Irradiation at 20 kHz of a solution of C_{60} in decahydronaphthalene results in the formation of $C_{60}H_2$.[65,66] The dihydrofullerene results from the reaction of C_{60} with hydrogen atoms generated by sonolysis of the solvent. In contrast with other hydrogenation methods,[67] sonication does not produce more highly hydrogenated derivatives. Moreover, continued irradiation results in the disappearance of both C_{60} and $C_{60}H_2$ from the solution, presumably by fragmentation into smaller hydrocarbons or by polymerisation.

The sonolysis of halocarbons is a typical case of a reaction which can be viewed with synthetic purposes, or for environmental remediation. As an example of the former, the sonolysis of carbon tetrachloride in methanol gives *in situ* hydrogen chloride which leads to the fast and selective deprotection of silyl ethers (Scheme 12). A simple evaporation of the solvent provides the pure desired products.[68]

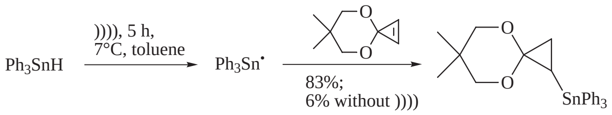
The chlorine atoms produced in this sonolysis were also used in a sonochemical modification of the Hunsdiecker preparation of alkyl halides *via* the thiohydroxamic esters,[69] and for the halogenation of sugars at the anomeric position.[70]

The sonolyses of other bonds have been reported, the most important cases are the Sn–H and P–H bonds. The former occurs without a radical initiator at unusually low temperatures



Scheme 12 Silyl ethers hydrolysis by *in situ* HCl.

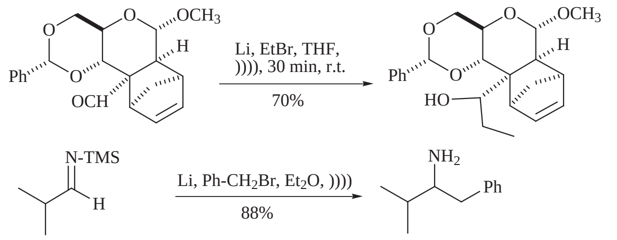
(Scheme 13). The tin-centred radicals add to unsaturated carbon–carbon bonds with stereoselectivities which are improved in comparison to conventional methods.[71] In the second case, the P-centred radical adds to imines, yielding aminophosphonic derivatives, used for phytosanitary applications.[72]



Scheme 13 Formation and addition of tin centered radicals.

Organometallic reagents

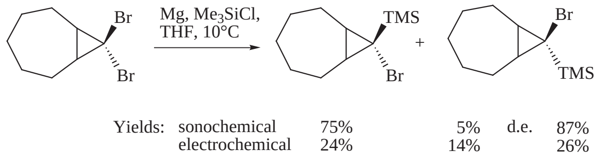
The formation of Grignard reagents involves a complex series of elementary steps next to or on the metal surface,[73] during which sonication should play a major role. Indeed, the preparation of lithium and magnesium reagents proceeds faster when sonication is applied,[74] but the yields are not greatly changed. The most interesting achievements in organometallic synthesis were obtained by using the one-step Barbier procedure. The reactions using lithium work very well and start almost immediately under sonication, whereas Barbier reactions with magnesium often require longer induction periods. Typical illustrations have been published,[75] with positive results even from benzylic halides (Scheme 14).[76,77] The procedure was applied successfully to *N*-(trimethylsilyl)imines.[78]



Scheme 14 Two examples of Barbier reactions.

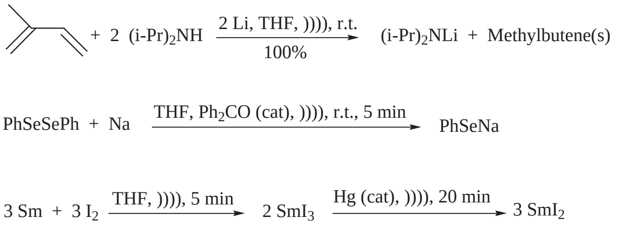
Using magnesium, the reductive coupling of a *gem*-dibromocyclopropane derivative with trimethylsilyl chloride occurs smoothly in high yields (Scheme 15). In this reaction, sonication induces changes in the stereoselectivity in comparison to the analogous electrochemical reduction.[79]

A sonochemical Reformatsky reaction was described recently,[80] but comparisons with the non-sonochemical process are not given. Other extensions of the Barbier reaction, such as the Bouveault reaction, have also been reported and used for the preparation of aldehydes and ketones.[81]



Scheme 15 Reductive silylation of a dibromocyclopropane.

A direct consequence of ultrasound-promoted ET is the facile preparation of radical anions and some other useful reagents, as illustrated here in the preparation of lithium amides in the presence of isoprene as an electron carrier (Scheme 16).[82] Sodium phenylselenide, the hydride ($(Ph_3P)CuH$), and the versatile samarium diiodide SmI_2 can be easily prepared by sonication upon addition of sodium/benzophenone.[83] Since the rate limiting step of these processes is ET from the metal surface, the initiation of the reaction is due to the presence of the ketyl radical anion, a fact that reinforces again the chemical role of ultrasound. The sonochemical preparation of SmI_2 can be conducted using a cleaning bath containing samarium metal and iodine in THF, which affords a yellow triiodide within 5 min. Further addition of a catalytic amount of mercury to the sonicated reaction leads to the desired reagent in quantitative yield. The overall process is completed in <30 min, in contrast with the classical protocols performed under an inert atmosphere, in dried solvents, and longer reaction times.[84]



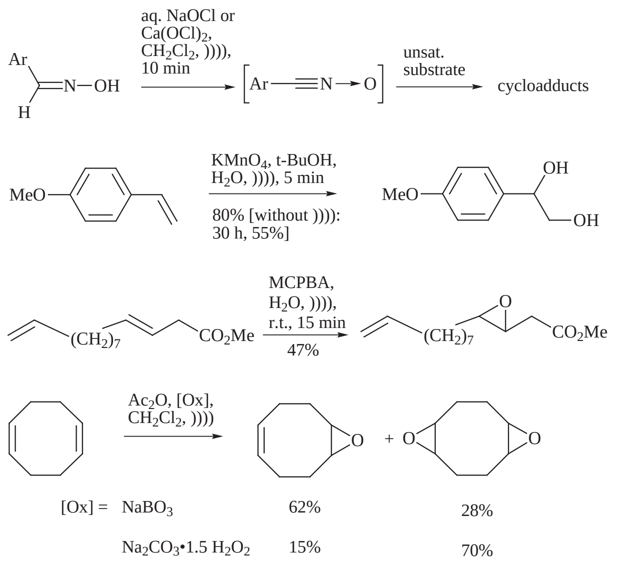
Scheme 16 Preparation of useful reagents by sonochemical reductive processes.

Safer reaction conditions

Oxidation and reduction reactions

Oxidation of organic compounds can still be relatively problematic, because of the toxicity of common oxidisers, their lack of selectivity or their instability in the presence of organic reductants. These drawbacks have stimulated the creativity of sonochemists. In preliminary studies, classical oxidisers were used, and sonication permits useful yields to be achieved, particularly in sugar and steroid chemistry.[85] In a second approach, new selectivities were found for cheap oxidisers, such as hydrogen peroxide,[86] sodium hypochlorite,[87] sodium percarbonate,[88] or even potassium permanganate.[3b] This latter reagent is used to effect the often difficult *cis*-*vic*-dihydroxylation of olefins (Scheme 17),[89] with the important advantage of replacing the toxic osmium tetroxide generally used in this reaction.

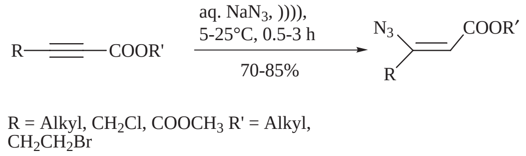
Sonication accelerates the epoxidation of long chain fatty esters with *m*-chloroperbenzoic acid (MCPBA).[90] This reaction can also be achieved using inexpensive sodium perborate or percarbonate in the presence of acetic anhydride in a biphasic solid–liquid system.[91] In the first case, the oxidising species is probably a peroxyboron compound, but percarbonate generates peracetic acid. From the diolefin 1,5-cyclooctadiene, some selectivity in favour of the mono or the diepoxy compound can be achieved by the proper selection of reagent.



Scheme 17 Sonochemical oxidations and epoxidations.

Additions

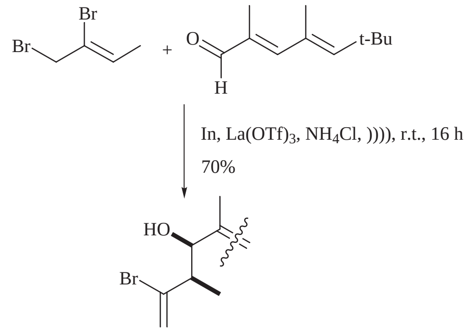
The addition of azide ions to 2-alkynoates occurs safely in an ultrasonically generated emulsion, much more efficiently than in the absence of ultrasound (Scheme 18).[92] Azide ions from the aqueous phase react with the substrate only at the interface. Ultrasonic exposure is important for good conversion despite the limited stability of the products, and in most cases no additional stirring is required.



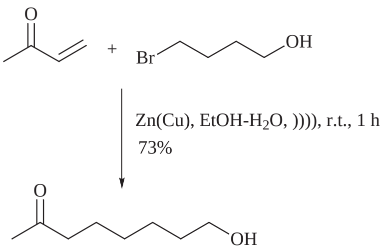
Scheme 18 Addition of azide to alkynes.

Improved safety conditions, especially for organometallic syntheses, are expected from the replacement of the traditional solvents by aqueous media. Since most organometallic species cannot survive in water, the intermediacy of some radical or radical anion on the metal surface itself is probably involved, as in the allylation reaction of carbonyls.[93] Originally, zinc and tin were used, but variations recently introduced in synthesis employ magnesium or indium. The stereochemical course of these reactions was examined and found to depend on the metal and the nature of the allylic halide.[94] Failures were observed with the less reactive 2-bromocrotyl bromide, but excellent reactivity was recovered by using indium as the metal in the presence of lanthanum triflate (Scheme 19).[95] Usually saturated halides do not react under these conditions, but noticeable exceptions are perfluoroalkyl iodides.[96] This procedure was applied to the preparation of modified carbohydrates.[97]

The conjugate addition of alkyl groups to activated double bonds do not necessarily proceed *via* the same mechanism, but from a similar idea: generating a reactive species insensitive to hydrolysis on the reaction time scale, and probably adsorbed on the metal surface, here the zinc–copper couple.[98] Applications to the syntheses of natural products have been reported.[99] An example is given below, leading to an intermediate in the synthesis of royal jelly (Scheme 20). Other similar uses of the couple, *e.g.* for epoxide ring opening, have been reported.[100]



Scheme 19 Addition of the 2-bromocrotyl group to an aldehyde.

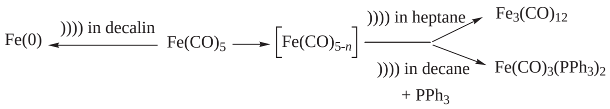


Scheme 20 A conjugate addition to methyl vinyl ketone in an aqueous solvent.

Preparation of micromaterials and nanostructures

Catalysis represents a highly efficient route to environmentally benign processes, and recent research has led to the discovery of more and more selective applications. The activity of a given catalyst can be modified by several methods, such as the formation of mixed compounds, insertion of selected atoms or doping and adsorption on solid supports, and in many cases depends on the physical state of the particles. Nanostructured compounds have rapidly appeared as promising,[101] and experts in the field logically turned their attention towards sonochemical methods for the preparation of new catalysts, colloids, amorphous and nano-crystalline solids.[102–104] The high temperatures and pressures created during the bubble collapse along with the rapid cooling rate ($>10^9$ K s^{-1}), much greater than those obtained by conventional melt quenching techniques (10^5–10^6 K s^{-1}),[105] enable the preparation of nanosized amorphous particles. The advantages of the faster cooling rates appear in the elaboration of amorphous metal oxides, because these compounds have thermal conductivities which are generally much lower than those of the metals making the conventional techniques unsatisfactory. When particle systems have sizes <10 nm, they are usually called colloids. Chemically prepared metal colloids are only stable in solution as they are protected by solvent molecules and electric charges preventing coagulation. Addition of natural or synthetic macromolecules confers a better stabilisation.[106]

Nanosized amorphous powders of transition metals and their alloys can be obtained by the sonochemical decomposition of volatile organometallic compounds,[102,107,108] following the pioneering work by Suslick and his group.[4a, 44a] A typical case of sonochemical switching was met with the sonolysis of iron pentacarbonyl. Pyrolysis and photolysis give pyrophoric iron and diiron nonacarbonyl respectively. In the non-volatile decalin solvent, cavitation energy is high, and sonolysis provides Fe(0). By increasing the vapor pressure, the cavitational energy can be tuned to the point at which a selective, stepwise ligand cleavage occurs, thus providing evidence of the effect of the solvent physical properties on the reaction yield. Accordingly, sonolysis in heptane gives triiron dodecacarbonyl, a compound not easily accessible by other methods. The coordinatively unsaturated $Fe(CO)_{5-n}$ species thus obtained (Scheme 21) reacts further with $Fe(CO)_5$ to give the final compound in 80% yield, or can be trapped by ligands (alkenes, phosphines, *etc.*), with rates ≈10^5 times higher than in the non-irradiated process.

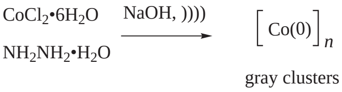


Scheme 21 Sonolysis of iron pentacarbonyl.

Using this model, the authors determined kinetically the temperature inside the bubbles (5200 K), and in the limit layer (1900 K).[109] Sonolytic reactions leading to metal colloids are performed under irradiation at 20 kHz in alkane solvents having a low volatility (*e.g.* decane). The nanosized iron colloid can be stabilised with a polymeric ligand like poly(vinylpyrrolidone) (PVP) under an oxygen-free argon atmosphere.[110] Structural analyses (by electron microscopy and diffraction) show that the iron particles in the polymeric matrix range from 3 to 8 nm in size, and the iron clusters are initially amorphous, although crystallisation to an α-Fe phase may be induced by irradiating the particles with a high-intensity electron beam or heating at ≈350 °C in N_2.[107,108] The Fe powder prepared contains ≈3% carbon and ≈1% oxygen as residual impurities and possesses a high surface area (≈120 $m^2\ g^{-1}$). Oleic acid, an unsaturated fatty acid, stabilises the colloid, while saturated stearic acid does not. The initially yellow solution of $Fe(CO)_5$ and oleic acid in hexadecane turns black after 1 h sonication. The colloid particles thus prepared are slightly larger than the PVP colloid (average size ≈8 nm), and electron diffraction after *in situ* crystallisation reveals that the particles in oleic acid are a mixture of Fe and FeO. Interestingly, these nanometer-sized iron particles are superparamagnetic.[111]

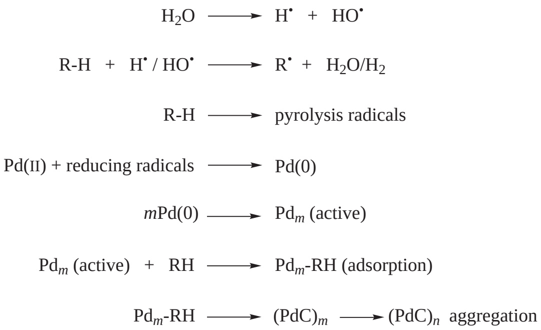
The Fe, Co, and Fe–Co alloys from $Fe(CO)_5$ and $Co(CO)_3(NO)$ have high activities for cyclohexane dehydrogenation and hydrogenolysis, and Fe supported on SiO_2 is an active Fischer–Tropsch catalyst.[107*a*] Ultrasound irradiation of $Mo(CO)_6$ gives nanometer-sized clusters (≈2 nm) of Mo_2C having a dehydrogenation activity comparable to that of ultrafine platinum powders.[102,108] The same sonolysis carried out in the presence of sulfur leads to nanometer-sized particles of molybdenum sulfide, MoS_2, an efficient hydrodesulfurisation catalyst. It is used to remove sulfur containing products from gasoline and other fossil fuels, with the purpose of reducing the formation of acid-rain-causing combustion gases.[112] Sonochemically prepared molybdenum sulfide is 10 times more active than RuS_2, a catalyst too expensive for large scale use.

Amorphous nickel powder has been prepared by sonochemical decomposition of $Ni(CO)_4$ as a neat liquid or in decalin solution,[113] and nanophase amorphous nickel supported on silica microspheres has been obtained as well.[114] A facile synthesis of cobalt nanoclusters has been reported recently,[115] by sonication of basic solutions containing Co(II) (Scheme 22), which is accompanied by a sudden color change from blue-violet to gray. The colloid consists primarily of cobalt, although a small amount of oxygen, possibly as a very thin oxide coating, is also present. The cobalt nanoclusters are ferromagnetic and may be useful in the construction of high-density recording media or permanent magnets.



Scheme 22 Sonochemical formation of cobalt nanoclusters.

The sonochemical preparation of noble metal particles and bimetallic nanoparticles in aqueous solutions has been performed by various groups.[116–120] Thus, the synthesis of palladium nanoparticles with interstitial carbon (PdC_x) can be achieved by the sonochemical reduction of an aqueous solution of tetrachloropalladade(II) in the presence of an organic additive.[120] The latter serves as an accelerator of the reduction of Pd(II). The formation of stable colloidal Pd particles proceeds *via* the equations depicted in Scheme 23.



Scheme 23 Formation of palladium nanoparticles by sonochemical reduction in the presence of an organic compound.

The reduction of Pd(II) is effected by the radicals generated through the sonolyses of water and the organic additive. The Pd clusters should be very reactive and the cleavage of an organic C–C or C–H bond can occur over the clusters at room temperature. Accordingly, in the subsequent steps, organic additives are adsorbed on the cluster surface, and finally carbon atoms on the particle surface diffuse in the Pd metal lattice. A nanostructured palladium powder can be prepared free of carbon by sonication of the acetylacetonate in toluene.[121]

The above methodology has also been applied to the preparation of colloidal dispersions of bimetallic nanoparticles of gold and palladium.[120*b*] An aqueous solution containing Au(III) and Pd(II) was irradiated at 200kHz in the presence of a surfactant. The latter not only has a stabilising effect but also enhances the reduction rate, presumably due to its sonolysis to reducing radicals at the cavitation bubble interface. Transmission electron microscopy (TEM) shows spherical particles with a geometric mean diameter of *ca.* 8 nm. Likewise, TEM and X-ray diffraction reveal a core–shell structure, a core of Au and a shell of Pd. The thickness of the palladium layer of a bimetallic particle is 0.8nm, corresponding to a few layers of Pd atoms.

These protocols were extended to the preparation of nanosized amorphous oxides. $NiFe_2O_4$ powder is obtained by sonolyses of $Fe(CO)_5$ and $Ni(CO)_4$ mixtures in decalin solution under an oxygen pressure of 100–150 kPa.[122] The superparamagnetic material is an agglomerate of particles with diameters <10 nm. Ultrafine powders of Cr_2O_3 and Mn_2O_3 (50–200 nm) have been prepared by the sonochemical reduction of aqueous solutions of ammonium dichromate and potassium permanganate, respectively.[123] Heating induces the crystallisation.

A continuous process based on hydrodynamic cavitation was employed to prepare a wide variety of metal oxides in grain sizes of 1–10 nm, such as iron oxide, bismuth molybdate, perovskites, platinum-loaded zeolite, and other ceramics and superconductors.[41*a*] The method uses a microfluidiser to generate hydrodynamic cavitation mechanically. The internal pressure of the liquid media is elevated from ambient to between 60 and 1700 bar. Each experiment utilises a precipitating agent that is constantly fed into the inlet of the high-pressure pump, where it interacts with a second recirculated solution. Nanocrystalline oxides of yttrium, cerium and transition metal elements (Ti, Zr, Cr, Co, Ni) have also been prepared by this method.[124]

Leaving the field of inorganic chemistry, a particular case of nanoparticles worthy of consideration is that of the proteinaceous microspheres. The application of ultrasound to the preparation of these biological materials, although in its infancy, shows promising capacities.[125] The sonochemical synthesis was performed from a variety of proteins such as serum albumin, haemoglobin, horseradish peroxidase, lipase and pepsin, by irradiation at 20 kHz in the presence of oxygen to afford microspheres with diameters of ≈2.5 mm and a shell thickness of ≈35 nm. The content of these microspheres can be a gas and either aqueous or non-aqueous solutions. Air-filled haemoglobin microspheres have many of the desired properties of a blood substitute, and are small enough to pass through the circulatory system. Sonication does not alter significantly the protein structure and microspheres retain their ability to bind oxygen reversibly with oxygen affinities similar to that of native haemoglobin. The formation mechanism under sonication involves both emulsification and chemical cross-linking of cysteine residues between protein molecules from the superoxide radical $HO_2^{\cdot}$, produced during the sonolysis of water in the presence of O_2. Evidence for superoxide formation in argon-saturated aqueous solutions has also been observed by Riesz and coworkers in the sonochemistry of cytochrome C.[126] Microsphere shells from peroxidase, lipase or pepsin have a significant enzymatic activity.

Conclusion

Ultrasound, through the unique phenomenon of cavitation, generates high-energy and/or excited state species, thereby inducing a cascade of radical and ET processes with subsequent bond breaking of compounds present in the solution. Remarkably, the extreme local conditions provided by the cavitational collapse occur in very short times, a few microseconds, which ensures an almost adiabatic process. Accordingly this chemistry performed in a conventional reaction flask with accessible technology can be utilised to drive mild alternative synthetic reactions with improved rates, yields and selectivities, the latter accounting for atom-economy transformations with reduced waste. Likewise, it is also possible to generate easily unusual reagents or reactive species, whose conventional formation requires more drastic conditions. This clean technology enables the preparation of new materials such as colloids, nanoclusters and protein microspheres. Last but not least, ultrasound research is finding new applications in environmental remediation, being able to decompose organic waste molecules.[127]

To reach the application stage, sonochemistry needs further study, especially in the field of chemical engineering.[128,129] An intrinsic difficulty is the non-homogeneous distribution of the energy,[130,131] since ultrasound propagates in the same manner as light. Then a reactor will contain sonicated and ‘dead’ volumes which must be minimized, *e.g.* by taking advantage of the reflection of the energy at the surface and on the walls *via* a proper reactor geometry. Cases exist where standing waves[132] can increase reaction rates. These specific aspects have motivated several chemical engineering studies and calculations of the acoustic field in a reactor have been made for homogeneous reactions, and heterogeneous systems as well.[133,134] Scale-up studies have been undertaken to check the industrial feasibility of ultrasonic pollutant destruction.[135] The advantage of using higher frequencies (*ca.* 500 kHz) is confirmed, together with the role of standing wave conditions. It can be anticipated that the developing field of the industrial application of sonochemistry will expand considerably when adequate use of cavitational energy is properly harnessed, for the profit of the new environmentally benign technologies.

Acknowledgements

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Environmental benefits of methanesulfonic acid:

Comparative properties and advantages

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Summary

This paper reviews some chemical and physical characteristics of methanesulfonic acid and the short-chain alkanesulfonic acids in general. The aqueous solubility of metal methanesulfonates, the conductivity of aqueous methanesulfonic acid (MSA) solutions and the low toxicity of MSA all make MSA(aq) an ideal electrolyte for many electrochemical processes, especially those involving tin and lead. Aspects of aqueous process effluent treatment, acid recovery and metal alkanesulfonate salt preparation are also environmentally favorable. Emphasis in this paper is given to rationalizing the rapidly growing commercial preference for MSA(aq) as an electrochemical electrolyte, especially with respect to the substitution of MSA for HBF_4 in the electroplating of Sn/Pb solder. Economic aspects of MSA are also considered.

Introduction

Methanesulfonic acid is the commercial electrolyte standard for the electroplating of Sn/Pb solder, and over the past 20 years MSA has largely replaced fluoroboric acid, the previous industrial standard, as the electrolyte of choice for electrochemical processes involving lead. MSA is also an emerging electrolyte choice for the electroplating of pure tin on sheet steel. The wide acceptance of methanesulfonic acid (MSA) as an acid electrolyte for electrochemical processes, especially those involving tin and lead, has resulted from a combination of diverse physical and chemical properties. These properties include high saturation metal salt solubilities, high conductivity, ease of effluent treatment and low relative toxicity. A full understanding of the functional and environmental benefits of MSA requires a simultaneous appreciation of several distinctly different subject areas. The authors have over the past 10 years developed a significant body of data related to a number of commercially significant aspects of MSA, and in this paper we have endeavored to present those properties of MSA which make it an advantageous electrolyte. This paper is not intended as a comprehensive review of the uses and/or properties of MSA, but rather it is intended to offer a reasonable explanation, largely based on work conducted at Elf Atochem, as to why MSA has become the electrolyte of choice in a number of electrochemical applications.

Criteria for selection of acidic electrolytes for electrochemistry

Electroplating processes typically involve the electrolytic deposition of a thin coating of a metal onto a conductive substrate.[1] Such processes are normally carried out in ionically conductive aqueous solutions, and such aqueous solutions are normally made conductive by the addition of acids, bases and/or neutral salts. In general, plating processes are classified according to the nature of the aqueous electrolyte (acid, base, neutral) employed. Acid based electrolytes are desirable in that they allow for very high solution conductivity and metal ion solubility. Consequently, a number of commercial electroplating processes (*e.g.*, Ferrostan™, Ronastan™, Techni Solder™, Solderon™, *etc.*) have adopted standard acid electrolytes.[1–3]

Certain metal salts, such as those of Cu, Ni and Sn, are soluble in most acid electrolytes (*e.g.*, H_2SO_4, HCl, HBF_4, $MeSO_3H$, *etc.*), and solubility considerations are not important in the selection of acid electrolytes for electroplating process involving such metals. Other metal salts, such as those of Pb and Ag, are only soluble in a limited number of acid electrolytes, and solubility considerations are paramount in the design of acid electrolytes for such metals. The high aqueous solubilities of metal salts of MSA make it an ideal electroplating electrolyte. The solubility advantage is particularly great for Sn(II), Hg(II), Pb(II) and Ag(I) salts. The saturation solubilities of some metal methanesulfonates (compounds **1**–**18**, preparative details are included in the Experimental section, listed in ascending order in Table 1), metal sulfates and metal chlorides are presented in Table 1.

Table 1 clearly shows the high solubility of the Ca(II), Sr(II), Ba(II), Ag(I), Sn(II), Pb(II) and Hg(II) salts of MSA relative to the corresponding salts of sulfuric acid. Also, the high solubility of the Ag(I), Pb(II) and Hg(II) salts of MSA relative to the corresponding salts of hydrochloric acid is clearly seen. The universal aqueous solubility of metal salts of MSA is similar to the

Green Context

The electroplating industry is a major user of chemicals. One concern which has been growing in the last few years is the use of acid electrolytes. This paper discusses the benefits to be gained from the use of methanesulfonic acid in electrochemical processes involving lead and tin. Effluent treatment, acid recovery and salt formation are all aspects of the process as a whole where the use of methanesulfonic acid is of environmental benefit. ***DJM***

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Table 1 The aqueous saturation solubility of some metal methanesulfonates, chlorides and sulfates at room temperature (22 °C)

Metal cation[a]	Aqueous saturation solubility (mol dm^{-3} as metal)[b]		
	Methanesulfonate	Sulfate	Chloride
NH_4^+	6.83	8.17	5.06
Li^+	7.06	4.90	9.37
Na^+	5.65	2.78	5.57
K^+	4.48	1.25	3.86
Mg^{2+}	1.40	2.63	5.02
Ca^{2+}	2.92	0.0249	5.51
Sr^{2+}	2.55	0	3.04
Ba^{2+}	1.59	0	1.71
Mn^{2+}	2.90	3.52	4.12
Co^{2+}	2.53	2.16	3.87
Ni^{2+}	2.13	2.44	4.38
Cu^{2+}	2.00	1.35	4.87
Ag^+	3.72	0.0556	0
Zn^{2+}	2.16	3.32	13.0
Cd^{2+}	3.20	3.10	5.71
Sn^{2+}	3.73	1.42	4.91
Hg^{2+}	1.81	0	0.239
Pb^{2+}	2.60	0	0.0338

[a] Preparations of the metal methanesulfonates (compounds **1**–**18**) are given in the Experimental section. [b] All measurements were made at Elf Atochem's King of Prussia Technical Center (see Experimental section).

universal aqueous solubility of metal salts of nitric acid and perchloric acid, but, as is shown throughout this article, MSA also offers a significant number of other advantages in addition to this universal aqueous metal salt solubility.

Some pertinent properties of methanesulfonic acid

The utility of methanesulfonic acid (MSA) in numerous application areas (esterification catalysts, alkylation catalysts, polymer solvents, electroplating, electrochemistry, *etc.*) derives from a number of physical and chemical properties which in combination are unique. For instance, MSA(aq) allows for excellent solubilization of metal salts and surface active agents. MSA has a low tendency to oxidize organic compounds. MSA is a strong acid ($pK_a = -1.9$)[4] which is almost completely ionized at 0.1 M in aqueous solution.[4] MSA(aq) solutions exposed to open atmospheric conditions display a unique stabilization of metal ions in their lower valence states, or, stated differently, MSA solutions allow for a unique resistance to the oxidation of metal ions to their higher valent states. This oxidative stability of metal ions in MSA(aq) solutions is perhaps best known for the Sn(II)/Sn(IV) system. Of all the common acid electrolytes, MSA based aqueous solutions of Sn(II) have displayed the highest stability known toward oxidation to Sn(IV).[5] The oxidation of tin(II) to tin(IV) causes an insoluble stannic sludge to form in the electrolyte, and such sludge is difficult to remove and waste-treat.

Comparative toxicity and environmental properties of MSA

The 'green' character of methanesulfonic acid, especially as compared to fluoroboric acid and fluorosilicic acid, is derived from several factors. In general, MSA is less toxic than fluoroboric acid and fluorosilicic acid. Fluoroboric acid has a reported LD_{50} (oral, rat) of 464–495 mg kg^{-1}, while MSA has a reported LD_{50} (oral, rat) of 1158 mg kg^{-1}.[6] In addition, fluoroboric acid and fluorosilicic acids have lachrymatory properties, and both acids can evolve HF. As a result of their tendency to evolve HF, fluoroboric acid and fluorosilicic acid have established OSHA PEL (permissible exposure limit) levels of 2.5 mg HF per cubic meter (8 h, TWA).[7] It has been found that HF levels in excess of the OSHA PEL can develop in the atmosphere surrounding fluoroboric acid and fluorosilicic acid solutions when ventilation is inadequate.[8] MSA has no established OSHA PEL, as MSA(aq) solutions do not, under normal conditions, evolve any dangerous volatile chemicals. In general, the low toxicity of MSA, especially when compared to HF complex acids like fluoroboric acid and fluorosilicic acid, makes it a safe electrolyte to handle.

MSA is considered readily biodegradable (OECD 303A, OECD 301D closed bottle, OECD 301A DOC Die-Away, BOD), ultimately forming sulfate and carbon dioxide. In fact, MSA is considered to be a natural product, and MSA is part of the natural sulfur cycle.[9] By contrast, discharged fluoroboric acid undergoes hydrolytic dissociation into boric acid and fluoride while discharged fluorosilicic acid undergoes hydrolytic dissociation into silicic acid (silica) and fluoride. In the case of fluoroboric acid, both fluoride and boron are environmentally troublesome, while for fluorosilicic acid, the fluoride is a problem. In general, the benign nature of MSA, especially when compared to HF complex acids like fluoroboric acid and fluorosilicic acid, makes it an environmentally advantageous electrolyte.

Comparative conductivity of methanesulfonic acid

Electrolyte conductivity is an important parameter in electroplating. Higher electrolyte conductivity leads to lower overall cell voltage, and a minimal cell voltage leads to a minimal electricity cost. The electrical cost of any electrochemical process can be given by the formula $EC = 3600\,kVI$ (EC = electrical cost of the process per hour, k = utility cost per joule, V = cell voltage in volts, I = cell current in amperes). Usually, the current is set equal to $(A_E)(CD_O)$, where A_E is the total electrode area and CD_O is the optimal current density for the process, and the utility cost is fixed by market conditions. Thus, minimizing electrical cost is tantamount to minimizing cell voltage, and one good way to minimize cell voltage is to maximize electrolyte conductivity. Note that saving money by consuming less electricity is both economically and environmentally beneficial. The environmental benefit derives from the consequent reduction in the use of fuel by the electricity generating utility company.

For comparison purposes, the equivalent conductance of 2, 1, 0.5, 0.1, 0.05 and 0.01 N aqueous solutions of H_2SO_4, HCl, $MeSO_3H$, $EtSO_3H$ and Pr^nSO_3H are given in Table 2.

The conductivity behavior of methanesulfonic acid (MSA), ethanesulfonic acid (ESA) and propanesulfonic acid (PSA) can be seen to be comparable to the conductivity behavior of other strong acids such as sulfuric acid and hydrochloric acid. While the conductivity displayed by MSA(aq) is not exceptional with respect to other strong acids, it is, in combination with MSA's other beneficial properties, another piece in the puzzle that explains the ever increasing commercial adoption of MSA(aq) as an electrolyte for electrochemical processes.

A Kohlrausch plot of the conductivity data given in Table 2 is presented in Fig. 1. The Kohlrausch plot allows for better visualization of the conductivity data. One interesting observation from the plot is the increased equivalent conductivity of MSA(aq) over H_2SO_4(aq) in the acid concentration range from 0.01 to 2 N.

Table 2 The equivalent conductance of aqueous solutions of some commonly available acids. Equivalent conductance values are reported in S cm^2 mol^{-1}

Acid	2 N	1 N	0.5 N	0.1 N	0.05 N	0.01 N
Hydrochloric	—	346.11	373.53	403.63	412.12	421.80
Sulfuric	413.84	444.88	464.12	529.08	572.76	699.40
Methanesulfonic	232.97	299.60	336.47	372.74	381.76	391.78
Ethanesulfonic	200.30	276.95	320.79	364.36	373.27	384.16
Propanesulfonic	187.96	268.06	314.88	361.26	370.65	382.20

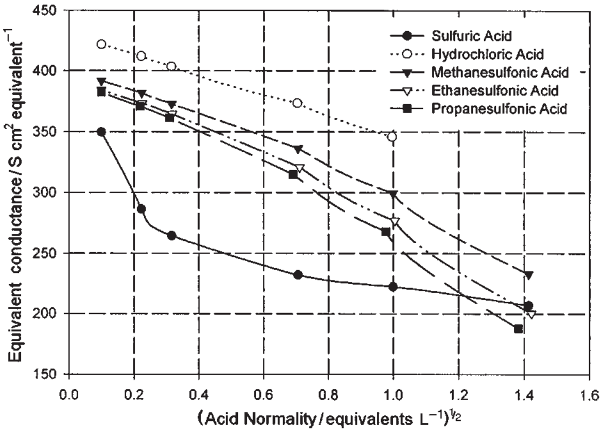

Fig. 1 A Kohlrausch plot of conductivity data for H_2SO_4(aq), HCl(aq), MSA(aq), ESA(aq) and PSA(aq). The conductivity values are also tabulated in Table 2.

Recovery of methanesulfonic acid from commercial processes

An electrowinning acid recovery method (designated by acronym as EWARE) which allows for the recovery of pure alkanesulfonic acids (*e.g.*, MSA) from corresponding metal alkanesulfonate salts has been developed. The process is based on electrowinning out of an anion-exchange membrane divided cell. The anode process is O_2/H^+ generation, and the cathode process is metal electrodeposition. The process is shown schematically in Fig. 2.

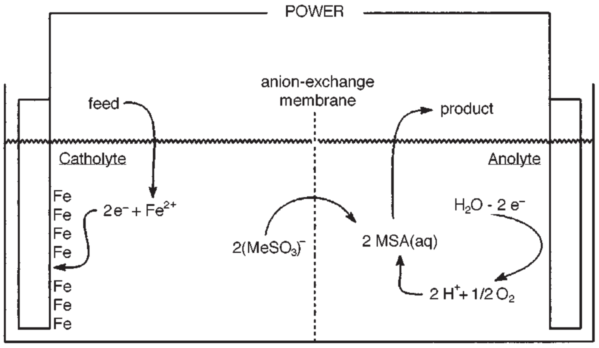

Fig. 2 Divided cell electrowinning for the recovery of MSA from $Fe(O_3SMe)_2$.

In Fig. 2, iron electrodeposition is the cathode process, O_2/H^+ generation is the anode process and methanesulfonate transport is the anion-exchange membrane process. The reduction of water to hydrogen and hydroxide competes with iron deposition at the cathode, but this competitive process does not necessarily reduce the efficiency of the acid recovery process. Only proton backleakage through the anion-exchange membrane reduces the overall efficiency of acid recovery. However, when the reduction of water becomes a significant portion of the overall cathode reaction, then metal oxide sludging, as opposed to metal electrodeposition, becomes the dominant catholyte process.

While conceptually similar processes are available for fluoroborate and/or fluorosilicate based electrolytes, there are a number of practical problems which plague systems designed to recover HBF_4 and H_2SiF_6 from waste streams. HBF_4 and H_2SiF_6 tend to dissociate into BF_3/HF and SiF_4/HF respectively, during transport through anion-exchange membranes. Such dissociation results in the formation of more mobile fluoride anions as compared to the bulkier fluoroborate and/or fluorosilicate anions. In addition, fluoroborate and fluorosilicate undergo hydrolysis reactions in alkaline solution, and acid recovery catholyte solutions often become alkaline during the recovery process. All things considered, the recovery of MSA from metal alkanesulfonate based waste is easier than the recovery of HBF_4 or H_2SiF_6 from metal fluoroborate and metal fluorosilicate waste, respectively.

The EWARE process can also be conducted in an undivided electrowinning cell operated in batch mode, but the use of an undivided cell often results in low collection efficiency and poor product quality. In the recovery of acid value from iron, cobalt and nickel salts (first row Group VIII transition metals), the performance of an undivided electrowinning cell is particularly poor (see electrowinning procedure 1 in the Experimental section). This is due to the low efficiency of electrodeposition of first row Group VIII metals from acidic solutions. Industrial waste solutions containing iron, nickel and/or cobalt salts are often slightly acidic, and a good recovery technique must be capable of recovering acid value from such acidic waste solutions. The anion-exchange membrane divided cell works well here because it allows for an initial increase of the waste stream pH (by cathodic base generation) up to a value at which metal deposition becomes practical. Once metal deposition begins, the pH increase is halted. Thus, the process is ‘self-stabilizing’ in nature. In the early stages of acid recovery by electrowinning from a solution of Fe, Co and/or Ni salts, very little metal is actually deposited on the cathode. Instead, base is produced on the cathode while acid is produced on the anode. The net result of the divided cell electrowinning process during this early stage is simply movement of acid from the cathode compartment to the anode compartment. After sufficient acid has been moved from the catholyte into the anolyte, the depositon of Fe, Co and/or Ni begins. While the use of an undivided cell is possible for waste streams which do not contain Fe, Co or Ni salts, it is generally better to use a divided cell process for all waste streams. The divided cell process allows for the recovery of pure acid with <10 ppm of metal contamination, while the use of an undivided cell produces acid with much higher residual metal contamination (see electrowinning procedure 1 in the Experimental section).

Anion-exchange membranes are thin sheets of polymeric material wherein the polymer structure contains fixed ammonium and/or amine groups distributed throughout the backbone. Furthermore, these anion exchanging ammonium groups are at least partially distributed in porous channels dispersed throughout the membranes structure. These porous channels are of molecular dimensions, and they are responsible for the selective transport of anions. For a more thorough discussion of ion permeable membranes see, for instance; T. A. Davis, J. D. Genders and D. Pletcher, *A First Course in Ion Permeable Membranes*, Alresford Press Ltd., UK, 1997. It is known that anion-exchange membranes have, under certain conditions, restricted stability and longevity. In particular, anion-exchange membranes are susceptible to chemical degradation in the presence of strong bases and oxidizing agents. Strong oxidants cause damage *via* oxidation of the amine/ammonium groups to amine oxides while strong bases cause damage *via* Hofmann type eliminations of amines from the polymer backbone. In the application discussed here, the anion-exchange membrane is not exposed to strong bases or oxidants. Thus, the average longevity of anion-exchange membranes in this application is equal to or greater than the average life of other durable membrane materials such as Nafion.

The divided cell process was optimized for use with both continuous anolyte and catholyte streams. The catholyte stream was an aqueous solution of a metal alkanesulfonate salt. In continuous mode, the catholyte stream was continuously recycled while being maintained at constant metal salt concentration by additions of solid salt and/or concentrate. The anolyte stream contained the generated alkanesulfonic acid product. In continuous mode, the anolyte stream was continuously removed while anolyte volume was made-up with deionized water. Cathodic metal deposits were removed on a regular schedule.

Continuous electrowinning was found useful for the recovery of pure alkanesulfonic acids from solutions of relatively pure metal alkanesulfonate salts. Alternatively, the same continuous electrowinning process could be used for the recovery of less pure acid from old, contaminated and/or off-specification alkanesulfonic acid based solutions containing dissolved metals, surfactants, organics, *etc.* (*e.g.*, electroplating solutions).[10] In some cases, the best results were obtained by the initial removal and partial purification of a metal alkanesulfonate salt prior to acid recovery. The removal and isolation of relatively pure metal alkanesulfonate salts from commercial solutions (*e.g.*, electroplating solutions) can be achieved *via* numerous methods including ion-exchange, selective crystallization and/or evaporation.

An application of particular importance involves alkanesulfonic acid recovery from iron(II) methanesulfonate. Iron(II) methanesulfonate is a by-product of iron removal from contaminated MSA-based strip steel tinplate solutions. The iron is removed by cooling the iron contaminated solutions followed by precipitation of iron(II) methanesulfonate. Iron contamination in acid tinplate solutions results from the unavoidable corrosion of the steel strip being plated. The dissolved iron introduced by corrosion catalyzes the air oxidation of tin(II) to tin(IV), with precipitation of tin(IV) from the tinplate solution as sludge. In order to minimize sludge formation, dissolved iron must be continuously removed. The removal of iron(II) methanesulfonate from MSA based acid tinplate solutions results in a loss of significant MSA value, and MSA recovery from the segregated iron(II) methanesulfonate is necessary for economic reasons. Both ion-exchange and continuous electrowinning processes can be used to recover MSA from iron(II) methanesulfonate, but continuous electrowinning is less difficult and provides for a purer product.

The use of electrowinning for the removal of metal ions from commercial effluent solutions and/or for the recovery of metal value from commercial leach solutions is well known. In environmental waste treatment applications, the process is optimized for the reduction of metal levels in effluent solutions. In commercial metal refining and recovery applications, the process is optimized for the production of pure metal. Additionally in many commercial refinery operations (*e.g.*, electrowinning of Zn), the recovery of impure acid for reuse as a leachant is also an important part of the overall process economics. Electrowinning in an anion-exchange membrane divided cell with both continuous anolyte and catholyte feeds, as described herein, is optimal for the generation of substantially pure acid for general reuse. The quality of the alkanesulfonic acid produced by the EWARE continuous electrowinning process is equivalent to the quality of the same alkanesulfonic acid as provided commercially by primary producers.

It is also possible to use continuous, divided cell electrowinning as part of a primary process for the manufacture of organic sulfonic acids. The oxidation of lead mercaptide compounds to lead alkanesulfonates with nitric acid has been reported.[11] Previous workers have converted such lead alkanesulfonates to free alkanesulfonic acid *via* precipitation of lead chloride following treatment with HCl. One could also use the electrowinning process described herein for the ultimate production of free alkanesulfonic acids (M = divalent metal cation), as shown in eqns. (1a) and (1b).[12]

$$(RS)_2M + 3\ O_2 \rightarrow (RSO_3)_2M \quad (1a)$$

$$(RSO_3)_2M + H_2O \rightarrow M + 2\ RSO_3H + 1/2\ O_2\ \text{(electrowinning)} \quad (1b)$$

Industrial production of fluoroboric acid, fluorosilicic acid and MSA

Fluoroboric acid is produced by the reaction of HF with boric acid, as shown in eqn. (2).[13]

$$4\ HF + H_3BO_3 \rightarrow HBF_4 + 3\ H_2O \quad (2)$$

The acid is typically sold as a 48% aqueous solution. The major markets for fluoroboric acid are as a plating electrolyte and as a raw material in the manufacture of fluoroborate salts. Iron(II) fluoroborate and lead(II) fluoroborate are produced for use in fluoroborate based Sn/Pb solder electroplating solutions. Potassium fluoroborate is produced for use in the preparation of aluminium master alloys. The preparation and use of fluoroboric acid and fluoroborate salts is hindered by the high toxicity of HF. Aqueous solutions containing HBF_4 tend to emit HF into the atmosphere surrounding them. Such HF emission can be diminished by the addition of boric acid, but low levels of HF in the work area can not be avoided.

Fluorosilicic acid can be produced by the reaction of HF with silica, as shown in eqn. (3).[14]

$$6\ HF + H_2SiO_3 \rightarrow H_2SiF_6 + 3\ H_2O \quad (3)$$

More commonly, fluorosilicic acid is obtained as a by-product of fluorophosphate mineral based production of phosphoric acid, as shown in eqn. (4).[14]

$$2[Ca_3(PO_4)_2 \cdot CaF_2] + 8\ H_2SO_4 + 16\ H_2O \rightarrow 8\ CaSO_4 \cdot 2\ H_2O + 4\ H_3PO_4 + 4\ HF \quad (4)$$

The HF produced *via* the above process reacts with silica also present in the mineral to produce a by-product stream of fluorosilicic acid. Anhydrous fluorosilicic acid dissociates almost instantaneously into SiF_4 and HF. At 19 °C and at aqueous concentrations between 60 and 70% by weight, fluorosilicic acid crystallizes as the dihydrate. Fluorosilicic acid is typically sold as a 25% aqueous solution. A major market for fluorosilicic acid is as a fluoridation agent for municipal water supplies. Other markets include lead refining and fluorosilicate salt manufacture. As with fluoroboric acid, the preparation and use of fluorosilicic acid and fluorosilicate salts is hindered by the high toxicity of HF.

Aqueous solutions containing H_2SiF_6, as for HBF_4(aq), continuously emit HF into the atmosphere surrounding them.

The development of commercial processes for the preparation of C_1 through to C_4 alkanesulfonic acids began in the 1940s with the work of Wayne Proell (Standard Oil of Indiana).[15] Proell's preparative method employed an initial NO_x catalyzed air oxidation of an alkyl mercaptan followed by a secondary stripping procedure which removed residual NO_x from the sulfonic acid product, as shown in eqn. (5).

$$2\ MeSH + 3\ O_2 \rightarrow 2\ MeSO_3H \qquad (5)$$

Proell also developed a number of applications of alkanesulfonic acids as alkylation catalysts,[16] as intermediates in the direct formation of sulfonate esters by reaction with olefins[17] and as electroplating electrolytes[18] with emphasis on copper plating.[19] Proell's early work in the field of sulfonic acid technology was both inspired and prolific, but his contributions were ahead of their time. It would not be until the early 1980s that a significant market for alkanesulfonic acids developed, and the first major customers turned out to be electronic components producers (*e.g.*, Intel, Motorola, AMD) who used MSA(aq) as an electrolyte for Sn/Pb solder electroplating.

The production of sulfonic acids by the air oxidation of mercaptans has the advantage of a very inexpensive oxidant (air), but the method suffers from several practical problems including poor product quality and the potential for explosions. The first practical short-chain alkanesulfonic acid preparation was developed by Pennwalt Corporation in 1967 (Pennwalt Corporation became part of Elf Atochem in 1989).[20] The Pennwalt method employed the direct chlorine oxidation of an aqueous emulsion of a mercaptan, as shown in eqn. (6).

$$RSH + 3\ Cl_2 + 3\ H_2O \rightarrow RSO_3H + 6\ HCl \qquad (6)$$

Several sulfonic acid preparations *via* anodic oxidation of mercaptans and/or disulfides have also been developed, but to date the economics have been prohibitive. Atochem has developed and patented a useful method for producing dialkanesulfonyl peroxides *via* the anodic oxidation of anhydrous alkanesulfonic acids.[21]

MSA in electrochemical processes involving lead

The design of acid electrolytes for the electroplating of Pb and Pb alloys, most importantly Sn/Pb, is dominated by solubility, performance and environmental considerations. Two important modern technologies depend integrally on the aqueous electrochemistry of lead; these are the electrodeposition of Sn/Pb solder in the electronics industry and the production of Pb acid batteries for the automotive industry. In addition, the refining of crude Pb obtained from mining and/or recycling operations is sometimes carried out electrolytically. As of today, only fluoroboric acid, fluorosilicic acid and methanesulfonic acid based electrolytes have been used with commercial success.[22,23]

Methanesulfonic acid is functionally and environmentally superior to fluoroboric acid (HBF_4), fluorosilicic acid (H_2SiF_6) and other HF complex acids (*e.g.*, HPF_6, $HSbF_6$) as an electrolyte for electrochemical processing. The advantages of MSA are evidenced by the recent (starting in about 1980 and continuing to today) substitution of MSA for HBF_4 in the commercially important electroplating of Sn/Pb solder. In this process, acidic aqueous solutions of Sn(II), Pb(II), free acid and surface active additives are employed. From these carefully formulated MSA based electroplating solutions, it is possible to produce solderable Sn/Pb coatings with specific properties (appearance, alloy content, thickness, ductility, *etc.*). Such engineered Sn/Pb coatings are, for example, deposited on the connecting pins of electrical devices, where they function to, among other things, protect the connecting pins from oxidation and the associated loss of solderability. Solderable Sn/Pb coatings are also sometimes electroplated onto printed circuit boards as part of the fabrication process, and Sn or Sn/Pb is electroplated onto wire as a solderable and corrosion inhibiting coating. A number of industrial electrochemical processes still employ fluoroboric and/or fluorosilicic acid based electrolytes. For many of these applications, active research programs aimed at replacing the HF complex acid with MSA are in place. In the electrorefining of lead, for instance, crude lead bullion anodes contained in an undivided electrochemical cell are electrolytically dissolved into and simultaneously cathodically redeposited, in purer form, from fluorosilicic acid based electrolytes. The substitution of MSA for fluorosilicic acid in the electrorefining of lead offers a number of functional and environmental advantages.[24] In both Sn/Pb solder electroplating and lead electrorefining, acidic aqueous solutions with a high concentration of Pb(II) ions are required.

Only certain acid electrolytes will allow for a high aqueous solubility of Pb(II) ions. These electrolytes include methanesulfonic acid (MSA, $MeSO_3H$), fluoroboric acid (HBF_4), fluorosilicic acid (H_2SiF_6), nitric acid (HNO_3), perchloric acid ($HClO_4$), chloric acid ($HClO_3$), acetic acid ($MeCO_2H$) and dithionic acid ($H_2S_2O_6$). The aqueous saturation solubilities of the relevant lead salts are shown in Table 3.

Table 3 Saturation solubility of some lead salts; temperature and solubility units in parentheses

Lead salt	Aqueous saturation solubility
Methanesulfonate, $Pb(O_3SMe)_2$	143 g per 100 g H_2O (25 °C)[a]
Fluoroborate, $Pb(BF_4)_2$	50 wt.% (20 °C)[b]
Fluorosilicate, $PbSiF_6{\cdot}4H_2O$	69 wt.% (20 °C)[c]
Nitrate, $Pb(NO_3)_2$	37 wt.% (25 °C)[d]
Perchlorate, $Pb(ClO_4)_2$	226 g per 100 g H_2O, 25 °C)[e]
Chlorate, $Pb(ClO_3)_2$	255 g per 100 g H_2O (25 °C)[f]
Acetate, $Pb(O_2CMe_3)_2$	55 g per 100 g H_2O (25 °C)[g]
Dithionate, $PbS_2O_6{\cdot}4H_2O$	115 g per 100 g H_2O (20 °C)[h]

[a] *MSA In Electrochemical Applications, Elf Atochem Technical Bulletin A-70-6*, 1991, p. 5. [b] Measurement made by Fidelity Chemicals Corporation of Newark, NJ, USA. [c] J. A. Gonzalez, PhD Thesis, University of British Columbia, *Electrochemical Processes Within the Slimes Layer of Lead Anodes During Betts Electrorefining*, 1991, p. 334. From: *Diss. Abstr. Int. B*, 1993, **53**, 4885. [d] A. A. Kazantsez, *Russ. J. Inorg. Chem.*, 1960, **5**, 773. [e] H. H. Willard and J. L. Kassner, *J. Am. Chem. Soc.*, 1930, **52**, 2391. [f] *Gmelin Handbuch der Anorganischen Chemie; Volume Pb*, 1969, vol. 1, p. 34. [g] M. L. Dundon and W. E. Henderson, *J. Am. Chem. Soc.*, 1922, **44**, 1196. [h] *CRC Handbook*, ed. R. Weast, Boca Raton, FL, 68th edn., 1987, p. B-101.

Various factors make the use of many of these 'solubility permissible' lead electrolytes untenable. For instance, the dithionate anion in lead dithionate is unstable at low pH, decomposing into sulfate and sulfite. Aqueous solutions of lead acetate in combination with acetic acid have insufficient conductivity to allow for high-speed electroplating operations. Lead chlorate, lead perchlorate and lead nitrate all tend to decompose cathodically, and the corresponding acids are very corrosive. Some of the problems with alternative Sn/Pb plating electrolytes are summarized below:

H_2SO_4, HCl	Precipitation of $PbSO_4$, $PbCl_2$
HNO_3	Cathodic decomposition of nitrate
$MeCO_2H$	Low conductivity
HBF_4, H_2SiF_6	Environmental problems H_2NSO_3H,
$H_2S_2O_6$	Hydrolysis problems, low conductivity

Complexation and hydrolysis; especially with respect to Pb(II)

The methanesulfonate ion forms less stable metal complexes than do the fluoroborate, fluorosilicate and associated fluoride ions.[22,25] The complexing nature of the fluoroborate, fluorosilicate and fluoride anions make it difficult to efficiently remove metal ions (*e.g.*, Pb^{2+}) from effluent streams. By far the most common method of dealing with metal containing aqueous effluent solutions is by caustic precipitation of metal oxide followed by filtration. The caustic precipitation of lead, for instance, is shown in eqn. (7) (X^- = any anion).

$$Pb^{2+} + 2\ X^- + 2\ NaOH \rightarrow PbO\ (s) + H_2O + 2\ NaX \qquad (7)$$

The insoluble lead oxide formed is removed from the aqueous effluent by filtration. The optimal conditions for caustic precipitation of metal ions vary depending on the metals present. For Pb(II), a pH of about 9 results in the maximum removal of lead *via* precipitation of the oxide. The amount of lead left dissolved in an aqueous effluent solution after caustic precipitation is strongly dependent upon the complexing nature of the anions present. A generic example of the competition between caustic precipitation of Pb(II) and anionic complexation of Pb(II) is shown in eqn. (8).

$$3\ Pb^{2+} + 6\ X^- + 4\ NaOH \rightarrow Na_4PbX_6 + 2\ H_2O + 2\ PbO(s) \qquad (8)$$

In eqn. (8), an octahedral distribution of ligands around Pb(II) is assumed. In practice, the actual structure of any lead complex formed will depend upon the nature of the anion X^- and the conditions present in the solution. Basically, the residual level of lead left in an effluent after a caustic precipitation operation is directly related to the complexing ability of the anions present in the effluent. The residual level of soluble Pb(II) left in solution after optimized caustic precipitation of lead from MSA(aq) based Sn/Pb plating solutions is less than 1 ppm, while the residual level of soluble Pb(II) left in solution after caustic precipitation of lead from HBF_4(aq) based solutions is typically more than 10 times as high.[26] Thus, caustic precipitation of $Pb(BF_4)_2$(aq) and/or $PbSiF_6$(aq) solutions leaves a significantly higher level of residual soluble lead than does caustic precipitation of $Pb(O_3SMe)_2$(aq) solutions. In addition, the residual lead level after caustic precipitation must be further reduced prior to discharge, and usually some sort of ion-exchange based technique is used for this purpose. As for the initial caustic precipitation process, the secondary removal of residual lead from treated HBF_4(aq) and H_2SiF_6(aq) solutions, as compared to treated MSA(aq) solutions, is also more difficult. In total, the lower toxicity and greater ease of waste treatment of MSA based solutions makes MSA the 'green' choice for commercial electrolytes, especially those containing lead.

Another problem with fluoroboric acid and fluorosilicic acid based electrochemical electrolytes is the tendency for these acids to be anodically hydrolyzed. Hydrolysis results in dissociation, and both processes are accelerated by the local acidification which inevitably occurs near the anode. Note that there are also hydroxide ion initiated hydrolysis reactions of fluoroboric acid and fluorosilicic acid, but such reactions are not important in acidic electrolytes. The dissociation of fluoroboric acid and fluorosilicic acid results in the production of the volatile species HF, BF_3 and SiF_4, and the hazards associated with these materials are well known (see Comparative Toxicity section of this paper). The simple dissociations of fluoroboric acid and fluorosilicic acid are shown in eqns. (9a) and (9b).

$$HBF_4 \rightarrow HF + BF_3(g) \qquad (9a)$$
$$H_2SiF_6 \rightarrow 2\ HF + SiF_4(g) \qquad (9b)$$

Fluoroboric acid is normally stabilized by the addition of an excess of boric acid (H_3BO_3), and fluorosilicic acid is normally stabilized by the addition of an excess of silicic acid (H_2SiO_3). These additives partially suppress the evolution of HF from fluoroboric and/or fluorosilicic acid based electrolytes, but the stabilizing effect is greatly compromised in the vicinity of the anode. Anodic acid generation creates local conditions which greatly accelerate HBF_4 and H_2SiF_6 decomposition. Such acidic anode conditions can be generated on both soluble anodes and insoluble anodes. By definition, soluble anodes are prepared from metals which will anodically dissolve into the electrolyte (*e.g.*, Sn/Pb electrodeposition processes normally employ soluble Sn/Pb anodes with a Sn/Pb composition which is similar to that present in the plating electrolyte). Insoluble anodes are prepared from materials which will not anodically dissolve into the electrolyte, and such anodes are designed to maximize the oxidation of a component in the electrolyte (*e.g.*, the oxidation of H_2O into O_2 and H^+, or the oxidation of Cl^- to Cl_2).

In addition to the dissociation caused by local anode acidification, there is also a catalytic acceleration of fluoroboric acid and fluorosilicic acid dissociation by many soluble anode slime layers. Soluble anodes which do not completely dissolve during electrolysis become covered with an insoluble residue which is commonly called a slime layer. Soluble anode slime layers are composed of residual poorly soluble impurities which were present in the original anode material. Soluble Sn/Pb anodes and crude lead bullion anodes, for instance, form slime layers. In the case of Sn/Pb electroplating, the formation of an anode slime layer is mostly an unavoidable inconvenience; while for lead electrorefining, the formation of a thick anode slime layer is an integral part of the basic process. In any event, both fluoroboric acid and fluorosilicic acid tend to dissociate within anode slime layers.[27] MSA, on the other hand, does not undergo anodic degradation as a result of local anode acidification and/or anode slime layer catalysis. Under the electrolysis conditions (current density, solution composition, *etc.*) normally employed for electroplating (*e.g.*, Sn/Pb electroplating) and electrorefining (*e.g.*, lead electrorefining), MSA is essentially completely stable (see electrowinning procedure 4, Experimental section).

Lead fluorosilicate, lead fluoroborate and lead methanesulfonate all possess good functional properties with respect to the electrochemistry of Pb(II) in aqueous solutions, and indeed these three electrolytes have been the standards for various electrochemical processes involving lead. In addition to functional properties, environmental and safety properties (known generically as 'green' properties) are also important, and since the early 1980s the superior 'green' character of MSA as compared to fluoroboric and fluorosilicic acid has become increasingly important.

The market for MSA in electrochemical processing

Methanesulfonic acid is a relatively new development in the world of electrochemical processing, having been made available commercially for the first time by Pennwalt Corporation in 1964.

In comparison, fluoroboric and fluorosilicic acid have been commercially available since the early 1900s. The late arrival of MSA was largely due to the relatively greater difficulty of preparing alkanesulfonic acids like MSA on a large scale, and MSA remained a technical curiosity until Pennwalt Corporation developed an industrial manufacturing process in 1964 (see references in the Industrial Production section above). Since the preparation of typical alkanesulfonic acids requires considerably greater effort than does the preparation of commodity acids (*e.g.*, H_2SO_4, HCl, H_2SiF_6), the price of alkanesulfonic acids is significantly higher than the price of commodity acids. The current price of some acids which allow for the convenient preparation of water soluble lead are shown in Table 4. The criterion of water soluble lead salts was used because electrochemical applications involving lead are the most significant for MSA.

Table 4 The current cost of some acids which yield soluble lead salts

Acid (commercial concentration)	Price quote ($\$$ lb^{-1}, absolute basis)	Source (date)
Acetic acid (99.7%), $MeCO_2H$	0.36	CMR[a] (1/22/99)
Fluoroboric acid (50%), HBF_4	1.05	CMR (1/22/99)
Fluorosilicic acid (318 g L^{-1}), H_2SiF_6	0.65	Cominco[b] (3/1/99)
Methanesulfonic acid (70%), $MeSO_3H$	2.20	Elf Atochem[c] (2/10/99)
Nitric acid (70%), HNO_3	0.10	CMR (1/22/99)

[a] *Chem. Mark. Rep.*, 1999, **255**, 28. [b] Quote, Cominco, Trail, BC, Canada (Consumer of Fluorosilicic Acid). [c] Quote, Elf Atochem NA, Philadelphia, PA, USA (Producer of MSA).

Conclusions

During the past twenty years, methanesulfonic acid ($MeSO_3H$) has largely replaced fluoroboric acid (HBF_4) as the electrolyte of choice for the electrodeposition of Sn/Pb solder on electronic devices. Certain other electrochemical processes involving lead, most notably the electrorefining of lead by the Bett's process, are currently carried out in fluorosilicic acid (H_2SiF_6) based electrolytes, but MSA based electrolytes are being actively investigated as environmentally superior alternatives to the currently used systems. Also, a number of commercial strip steel tin plating operations have recently converted to MSA based tin plating electrolytes.[28] There are also developing markets for MSA in Ag,[29] Ni,[30] Cu[31] and Zn[32] electroplating. These changes have been driven by the superior functional properties and environmental advantages of methanesulfonic acid (MSA).

The benefits of MSA(aq) include:

1. Excellent metal salt solubility
2. Excellent conductivity
3. Ease of effluent treatment
4. Stability
5. Low toxicity and biodegradability

With respect to electrochemical processes involving lead, MSA based process electrolytes are particularly advantageous in that they are less toxic and easier to waste treat than the existing alternatives. Into the foreseeable future, industrial electrochemical processes, especially those involving tin and lead, will likely continue to be converted to safe, functional, efficient and environmentally friendly MSA.

Experimental

Methanesulfonic acid (MSA) [75-75-2] and ethanesulfonic acid (ESA) [594-45-6] were obtained as 70% aqueous solutions from Elf Atochem NA. Hydrochloric acid and sulfuric acid were purchased from Aldrich Chemical Company. All chloride, sulfate, hydroxide and carbonate salts were purchased from Aldrich Chemical Company (Milwaukee, Wisconsin, USA).

Propanesulfonic acid (PSA) [226-114-2]

Prepared from propanesulfonyl chloride (PSC) [10147-36-1]. Crude PSC was obtained from Elf Atochem NA. The crude PSC was distilled (bp = 85 °C, 17 mm) to improve its purity (98% after distillation). The reaction was carried out by vigorously mixing H_2O (500 g) and PSC (1000 g) while slowly increasing the reaction temperature (*ca.* 1 °C min^{-1}) to *ca.* 110 °C. Care should be taken to insure that the reaction temperature is not increased too quickly, as the reaction can 'take-off'. If the reaction starts to overheat, then some control can be gained by slowing the stirring rate. While we had no trouble adding all the reactants together at once, one can for added control add the PSC to the reaction in small portions. After the initial heating, the hydrolysis was continued at 110 °C for 4 h, during which time evolved HCl was absorbed in a caustic trap. The crude 70% PSA(aq) which resulted was then heated with stirring to 100 °C under aspirator vacuum (*ca.*1 40 mmHg) for several hours to remove residual HCl. Nitrogen was bled (*ca.* 1 cm^3 s^{-1}) through the system to both assist in the removal of HCl(g) and to prevent darkening of the product. Occasional additions of doubly ionized (DI) H_2O were used to make up for volume lost during the HCl stripping process. After HCl removal was complete, the PSA(aq) was cooled slightly and *ca.* 4 mL of 30% H_2O_2(aq) per liter of 70% PSA(aq) was added to decolorize and deodorize the final product. The peroxide treated PSA(aq) was heated to 100 °C for several hours (under a nitrogen gas blanket) to guarantee complete destruction of residual peroxide (at room temperature, low levels of H_2O_2 can persist for months in 70% aqueous PSA). Typical PSA(aq) analysis was: clear color, no odor, no observable particles, assay = 70% w/w, density = 1.2 g cm^{-3}, molarity = 6.7 M (5.6 meq. PSA per g solution), sulfate level (by ion chromatography) = 70 ppm, chloride level (by IC) = 30–2000 ppm (depending on HCl stripping conditions), organic extractable impurities (CH_2Cl_2 extraction, by GC) = 50–2000 ppm (depending on H_2O_2 post-treatment conditions), residual PSC (CH_2Cl_2 extraction, by GC) = 0–1000 ppm (depending on hydrolysis conditions), residual peroxide (by titration) = 0–250 ppm (depending on H_2O_2 destruction conditions).

The preparative procedures for the alkanesulfonate salts are given below. Note that in most cases the salts were washed with solvents (*e.g.*, acetone, isopropyl alcohol, diethyl ether). The solvent volumes used (not specified below) were in all cases minimal. Generally a volume of acetone and/or isopropyl alcohol equal to the volume of the solid produced was employed, and a volume of ether equal to about 1/3 of the volume of solid produced was employed. All used wash solvent was disposed of in an appropriate manner. The initial solvent wash (acetone or isopropyl alcohol) was employed to remove excess sulfonic acid. This solvent wash could be avoided when time was available for careful aqueous recrystallization of the product. The second solvent wash (ether) was used to facilitate drying. The second solvent washing was not necessary when sufficient time was available to dry the product in a vacuum oven. Note that ether is very flammable, and the use of all solvents, especially ether, should only be undertaken by individuals with knowledge of the hazards involved. The solvent washing steps were employed as a convenient way to prepare small amounts of pure salts in a short period of time. Methods involving aqueous recrystallization and vacuum drying would certainly be more environmentally acceptable for the production of large amounts of material. In all cases, the identity and purity of the metal methanesulfonate product was established by % metal and % sulfur (methanesulfonate) analysis (AA spectroscopy and/or ICP/emission). In certain cases, IC analysis was used to corroborate the AA/ICP results. As the salts were often isolated as hydrates with non-stoichiometric amounts of associated water, the purity analysis was most conveniently reported in terms of the ratio of % metal to % sulfur (methanesulfonate). Note that this ratio is easily calculable by the following formula; (% metal / % sulfur) = [GMW(metal)]/[metal valence × 32.06(GMW of S)] (GMW = gram molecular weight).

Ammonium methanesulfonate [22515-76-0] 1

Equimolar amounts of MSA (1 mol of MSA as a 70% aqueous solution) and ammonia (1 mol of NH_3 as a 29% aqueous solution) were reacted together at room temperature. Water was removed from the reaction mixture *in vacuo* (4 mmHg), and the crystalline residue was washed with a small amount of isopropyl alcohol and ether. The solid product was reduced to a constant weight *in vacuo* (1 mmHg). Theoretical yield = 112 g, actual yield = 98 g (87%).

Lithium methanesulfonate [2550-62-1] 2

Lithium hydroxide monohydrate (42 g, 1 mol) was slowly added to 70% MSA (aq, 140 g, 1 mol) over 10 min with stirring. The homogeneous solution was reduced *in vacuo* (4 mmHg) to a solid residue, and the solid residue was washed with acetone and ether (to remove excess MSA). The solid product was reduced to a constant weight *in vacuo* (1 mmHg). Theoretical yield = 102 g, actual yield = 83 g (81%). For LiOMs; %Li/%S (theoretical) = 0.22, %Li/%S (actual) = 0.21.

Sodium methanesulfonate [2386-57-4] 3

Available from Aldrich Chemical Company. Reported purity of 98%.

Potassium methanesulfonate [2386-56-3] 4

Prepared with a method similar to that used for the preparation of the lithium salt of MSA except that isopropyl alcohol was used in place of acetone. Theoretical yield = 134 g, actual yield = 118 g (88%). For KOMs; %K/%S (theoretical) = 1.22, %K/%S (actual) = 1.20.

Magnesium methanesulfonate [62512-10-1] 5

Solid magnesium hydroxide (30 g, 0.51 mol) was slowly added to 70% MSA (aq, 142 g, 1.03 mol, 1% excess, heated to 80 °C, keep the solution temperature below 90 °C during addition). A small amount of DI H_2O (10 ml) was added to clarify the solution, and then the solution was allowed to cool to room temperature. $Mg(O_3SMe)_2$ precipitated from the solution upon cooling. The crystalline product was collected by vacuum filtration and washed with isopropyl alcohol and ether. The product was evaporated to constant weight *in vacuo* (1 mmHg). Theoretical yield = 214.5 g, actual yield = 123 g (57%). For $Mg(O_3SMe)_2·9H_2O$; %Mg/%S (theoretical) = 0.38, %Mg/%S (actual) = 0.37.

Calcium methanesulfonate [58131-47-8] 6

A 1 L beaker was charged with 70% MSA (aq, 310 g, 2.26 mol, 3% excess, heated to 90 °C). Finely powdered $CaCO_3$ (110 g, 1.10 mol) was added with stirring over *ca.* 1 h. Small additions of DI H_2O were used to wash solid $CaCO_3$ down the sides of the beaker. When the addition was complete, the temperature of the solution was brought to 100 °C and DI H_2O was added until the solution became clear. The clear solution was decanted away from solid particulates and then evaporated *in vacuo* (4 mmHg) to give a crystalline residue. The crystalline residue was washed with isopropyl alcohol and ether. The solid product was evaporated to constant weight *in vacuo* (1 mmHg). Theoretical yield = 253.1 g, actual yield = 94.1 g, (37%). For $Ca(O_3SMe)_2$; %Ca/%S (theoretical) = 0.63, %Ca/%S (actual) = 0.62.

Strontium methanesulfonate 7

A 500 mL beaker was charged with 70% MSA (aq, 75 g, 0.547 mol, 40% excess), powdered strontium carbonate (25 g, 0.160 mol), and DI H_2O (20 mL). The mixture was stirred overnight and then filtered through a 1 μm glass microfiber pad. The clear filtrate was evaporated *in vacuo* (4 mmHg) to a crystalline residue. The crystalline residue was washed with isopropyl alcohol and ether. The solid product was evaporated to constant weight *in vacuo* (1 mmHg). Theoretical yield = 44.4 g, actual yield = 42.1 g (95%).

Barium methanesulfonate [26755-96-4] 8

A 1 L beaker was charged with 70% MSA (aq, 274 g, 2 mol) and powdered barium carbonate (197 g, 1 mol). The mixture was stirred and heated (80 °C) while an additional portion of 70% MSA (aq, 100 g, 36% excess) was slowly added. After 1 h, enough DI H_2O was added to produce a homogeneous solution at 80 °C. A 50 ml dose of isopropyl alcohol was then added, and the still clear solution was allowed to cool to room temperature. The crystalline precipitate was collected by vacuum filtration and washed with isopropyl alcohol and ether. The solid product was brought to constant weight *in vacuo* (1 mmHg). Theoretical yield = 327.3 g, actual yield = 235 g (72%). For $Ba(O_3SMe)_2$; %Ba/%S (theoretical) = 2.14, %Ba/%S (actual) = 2.16.

Mn(II) [88576-27-6] 9, Co(II) [50910-89-9, dihydrate] 10, Ni(II) [55136-38-4] 11 and Cu(II) [54253-62-2] 12 salts of MSA

All prepared from the corresponding carbonates using methods similar to those described above. In some cases, filtration of an aqueous solution of the product was necessary [*e.g.*, to remove MnO_2 from $Mn(O_3SMe)_2$]. For $Mn(O_3SMe)_2·2H_2O$; %Mn/%S (theoretical) = 0.86, %Mn/%S (actual) = 0.87. For $Co(O_3SMe)_2·4H_2O$; %Co/%S (theoretical) = 0.92, %Co/%S (actual) = 0.92. For $Cu(O_3SMe)_2·4H_2O$; %Cu/%S (theoretical) = 0.99, %Cu/%S (actual) = 0.98.

The preparation of silver methanesulfonate was accomplished by each of the general methods discussed above. All four procedures are given below for comparative purposes.

Silver(I) methanesulfonate [2386-52-9] 13

From Ag_2O

To 500 g of 70% MSA (aq, 3.64 mol) in a 1 gallon beaker, 402 g of silver oxide (3.47 mol of Ag^+) was slowly added over 30 min so as to form a uniform suspension. The temperature of the reaction mixture rose to *ca.* 60 °C during the addition, and this temperature was maintained with heating for an additional 4 h. The reaction mixture was filtered through a thick 1 μm glass microfiber pad, and the filtrate was stripped *in vacuo* (4 mmHg) to a solid residue. The solid residue was washed with isopropyl alcohol and ether. Finally the crystalline product was reduced to constant weight *in vacuo* (1 mmHg). Theoretical yield = 704 g, actual yield = 450 g (64%). For Ag(OMs); %Ag/%S (theoretical) = 3.36, %Ag/%S (actual) = 3.37.

From ligand metathesis between MSA and $AgNO_3$

Note that the following procedure is given for informational purposes only. This method would not normally be recommended for the preparation of AgO_3SMe. Nitrate salts can be dangerous, and while we experienced no problem with this preparation it is still recommended that the entire procedure be conducted behind an explosion shield. A 100 mL round bottomed flask was charged with $AgNO_3$ (17.25 g, 101 mmol) and 70% MSA (14.5 g, 106 mmol). The flask was fitted with a condenser and 100 mL receiving flask. The receiving flask was ice cooled. The reaction mixture was stirred and put under aspirator vacuum (14 mmHg). The stirred reaction solution was gently heated to 90 °C and then left at this temperature for several hours during which time nitric acid distilled into the cooled receiving flask. After most of the nitric acid distilled over, the flask, still under vacuum, was heated further to an ultimate temperature of 170 °C. The flask was then cooled and the solid AgO_3SMe product removed. The crude product was washed with some acetone and ether to yield a final product with <100 ppm of residual nitrate. The yield was close to 100%. Overall purity as described above for AgO_3SMe produced from Ag_2O.

From chemical oxidation of Ag metal[33]

Hydrogen peroxide (93 mmol, 2 × excess) was added to a stirred mixture of silver metal (10 g, 93 mmol) in 20 mL of 70% MSA (aq) at such a rate that the temperature during the addition was kept below 45 °C. Following peroxide addition, the solution was stirred and the solution temperature maintained at 35 °C. A drop of the solution was tested at regular intervals for unreacted oxidant (iodide/starch color test). After all the oxidant had been consumed (reaction time strongly dependent on the surface area of the silver used), an additional portion of hydrogen peroxide (93 mmol) was added as before. Again, the solution was stirred and the solution temperature maintained at 35 °C. Following consumption of the second portion of oxidant, the reaction mixture was vacuum filtered through a 1 μm glass filter pad. The time-averaged rate of the reaction, under the conditions listed above, was *ca.* 1 mg Ag dissolution per hour per cm^2 of silver surface area. The higher the specific surface area ($cm^2\ g^{-1}$) of the metallic silver employed, the greater the absolute rate of the oxidative dissolution. With very fine silver powders (350 mesh and finer), the reaction evolved enough heat to create a need for vigorous cooling during the initial peroxide addition and throughout the reaction. The reaction time for fine silver powders was normally several hours. Note that reaction temperatures above 50 °C led to excessive decomposition of the hydrogen peroxide. With silver powders of intermediate fineness (*ca.* 100 mesh), the reaction took about 18 h. With silver chunks cut from a slab, the reaction was too slow to be be considered convenient. The consumption of the silver was between 10 and 95% depending on the fineness of the silver and the exact conditions employed. The reaction yield was close to 100% relative to the silver consumed. The reaction yield was between 10 and 45% relative to the hydrogen peroxide consumed, depending on the exact conditions employed. Purity as described above for AgO_3SMe produced from Ag_2O.

From anodic oxidation of Ag metal

An anion-exchange membrane (50 cm^2, ESC-7001, available from the Electrosynthesis Company, Lancaster, NY, USA) divided electrochemical tank cell (homemade) with a 1 L anolyte and catholyte compartment was fitted with a 60 cm^2 (one side) Ag anode and a 60 cm^2 (one side) Ni cathode (inter-electrode distance = 6 cm). The anolyte chamber was charged with 1 kg of 2% MSA(aq) wt/wt, and the catholyte chamber was charged with 1 L of 25% MSA(aq) wt/v. The anode process was oxidative silver dissolution. The cathode process was hydrogen formation. The membrane process involved passage of methanesulfonate from the catholyte into the anolyte. A current of 4 A (*ca.* 5 V) was passed for 6 h, and then the current was dropped to 1 A (*ca.*. 3 V) for 14 h (overnight). Note that the temperature of the solution increased over 2 h to a final steady 33 °C. The conductivity of the cell decreased throughout the experiment. The current was stopped, and the anolyte was removed and evaporated to yield a solid. The solid was washed with a small amount of acetone and ether. The final weight of AgO_3SMe was 218 g (76% current efficiency). Purity as described above for AgO_3SMe produced from Ag_2O.

Zn(II) [33684-80-9] 14, Cd(II) [74440-47-4] 15 and Sn(II) [53408-94-9] 16 salts of MSA

All prepared from the corresponding oxides using methods similar to those described above. Care should be taken in the preparation of tin(II) salts to exclude oxygen, as oxidation of Sn(II) to Sn(IV) can be troublesome. For $Zn(O_3SMe)_2{\cdot}2H_2O$; %Zn/%S (theoretical) = 1.02, %Zn/%S (actual) = 1.03. For $Sn(O_3SMe)_2{\cdot}2H_2O$; %Sn/%S (theoretical) = 1.84, %Sn/%S (actual) = 1.84.

Mercury(II) methanesulfonate [54253-64-4] 17

It should be noted that mercury compounds are highly toxic and proper protective equipment and procedures must be used at all times. The preparation of small amounts of this salt by the reaction of MSA(aq) with HgO was inconvenient. Instead, the target compound was obtained by heating an equinormal mixture of $Hg(NO_3)_2$ and 70% MSA(aq) under vacuum (30 mmHg, Teflon lined vacuum pump, caustic trap on the outlet of the pump). The temperature of the stirred mixture was slowly raised to *ca.* 100 °C (T_{max} = 110 °C), and the heating was continued for several hours until all the nitrate was removed as nitric acid. Though no tendency for energetic decomposition was noted, it is known that certain nitrate compounds can be unstable. As a precaution, the reaction apparatus was placed behind an explosion shield. The residual nitrate level in the final product was <300 ppm. Note that this procedure was employed with care and only used for the preparation of small amounts (5 g or less) of mercury(II) methanesulfonate. For $Hg(O_3SMe)_2$; %Hg/%S (theoretical) = 3.13, %Hg/%S (actual) = 3.12.

Lead(II) methanesulfonate [17570-76-2] 18

Prepared from $PbCO_3$ using a method similar to those described above. For $Pb(O_3SMe)_2$; %Pb/%S (theoretical) = 3.24, %Pb/%S (actual) = 3.21.

The following salts were used in the undivided cell electrowinning experiments.

Palladium(II) methanesulfonate [74109-53-8] 19

In a 50 mL beaker, 350 mesh palladium powder (1.06 g, 10 mmol), 70% MSA(aq) (2.72 g, 2 mL, 20 mmol) and 1.4 g of conc. HNO_3 (aq) (1 mL, 16 mmol) were mixed. The reaction was initiated by addition of one drop of conc. HCl(aq). The solid suspension rapidly turned dark brown, and the reaction was complete within 30 min. Further work-up could result in a solid product, but we opted to use a diluted solution, [Pd] = 5 g L^{-1}, of the crude reaction product directly in the next step (see electrowinning section of the Experimental section).

Copper(II) propanesulfonate [25321-66-8, tetrahydrate] 20

A 1 L beaker was charged with 200 g of 71% aqueous propanesulfonic acid (1.14 mol). To this was slowly added 63 g of basic copper carbonate (0.285 mol, 1.14 equiv) suspended in 100 mL of DI H_2O (final solution pH = 1.0). The solution was stirred at room temp. for 2 h and then filtered through a 1 μm glass microfiber pad. The filtrate was stripped *in vacuo* (4 mmHg) to a solid residue, and the residue washed with acetone and ether. The solid product was taken to constant weight *in vacuo* (1 mmHg). Theoretical yield = 176 g, actual yield = 162 g (92%).

Tin(II) ethanesulfonate [72437-74-2] 21

A 2 L flask was charged with 600 g of 70% aqueous ESA (3.81 mol, 3% excess) and then sparged with nitrogen gas. A 250 g portion of SnO (1.85 mol, 3.7 equiv.) was added with stirring and gentle N_2(g) sparging over 60 min. The reaction temperature increased from 23 to 30 °C during the addition. After stirring for 4 h under N_2(g), the solution was filtered through a 1 μm glass microfiber pad. The filtrate was stripped to dryness *in vacuo* (3 mmHg), and the solid residue was washed with acetone (isopropyl alcohol dissolves too much product) and ether. The product was taken to constant weight *in vacuo* (1 mmHg). Theoretical yield = 626 g, actual yield = 200 g (32%). The yield was low owing to losses in the rinse. Further product could be obtained by stripping the rinse solvents. For $Sn(O_3SEt)_2$; %Sn/%S (theoretical) = 1.85, %Pb/%S (actual) = 1.83.

Nickel(II) propanesulfonate 22

A 2 L beaker was charged with 303 g of aqueous 70% PSA (1.70 mol) and heated to 50 °C. To this solution was slowly added 100 g of nickel carbonate hydroxide tetrahydrate (0.17 mol, 0.85 mol of Ni^{2+}, 1.70 equiv.) slurried with 100 ml of DI H_2O. After 4 h at 50 °C, the solution was cooled and filtered through a 1 μm glass microfiber pad. The filtrate was stripped *in vacuo* (4 mmHg) to a solid residue, and the solid residue was washed with acetone and ether. The solid product was taken to constant weight *in vacuo* (1 mmHg). Theoretical yield = 518 g, actual yield = 330 g (64%).

Cobalt(II) ethanesulfonate [50910-90-2, dihydrate] 23

A 1 L beaker was charged with 172 g of aqueous 70% ESA (1.09 mol), and to this was added 50.6 g of $Co(OH)_2$ (0.54 mol, 1.08 equiv.). The temperature rose from room temperature to 50 °C during the addition. The suspension was stirred overnight at room temperature and then filtered through a 1 μm glass microfiber pad. The filtrate was reduced *in vacuo* (3 mmHg) to a solid residue. The solid residue was washed with isopropyl alcohol and ether. The purified product was reduced to constant weight *in vacuo* (1 mmHg). Theoretical yield = 150 g, actual yield = 147 g (98%). For $Co(O_3SEt)_2$; %Co/%S (theoretical) = 0.92, %Co/%S (actual) = 0.92.

Cadmium(II) propanesulfonate 24

A 1 L beaker was charged with 210 g of 71% aqueous PSA (1.20 mol). To this was slowly added 100 g of $CdCO_3$ (0.58 mol, 1.16 equiv.) slurried with 100 ml of DI H_2O. After 2 h, the solution was filtered through a 1 μm glass microfiber pad. The filtrate was stripped *in vacuo* (4 mmHg) to a solid residue. The solid residue was washed with acetone and ether. The solid product was taken to constant weight *in vacuo* (1 mmHg). Theoretical yield = 208 g, actual yield = 104 g (92% yield).

Iron(II) methanesulfonate [56525-23-6] 25

A 1 gallon beaker was charged with 1.5 kg of 70% aqueous MSA (10.9 mol). To the well stirred solution was added 250 g of iron powder (4.5 mol, Aldrich, 10 μm 99.9%) in 8 g portions over 6 h (ensure adequate ventilation to remove the hydrogen gas formed). The solution was stirred at room temperature overnight and then filtered through a 1 μm glass microfiber pad. The final product was an aqueous solution with [Fe] = 67.2 g l^{-1} and free acidity = 0.50 M.

Zinc(II) propanesulfonate 26

A 2 L beaker was charged with 450 g of 70% aqueous PSA (2.54 mol). To this was slowly added 100 g of ZnO (1.22 mol, 2.44 equiv.) slurried with 100 ml of DI H_2O. After 6 h, the solution was filtered through a 1 μm glass microfiber pad. The filtrate was stripped *in vacuo* (4 mmHg) to a solid residue. The solid residue was washed with acetone and ether. The solid product was taken to constant weight *in vacuo* (1 mmHg). Theoretical yield = 380 g, actual yield = 360 g (95%).

Zinc(II) ethanesulfonate [154780-19-5] 27

A 2 L beaker was charged with 550 g of 70% aqueous ESA (3.5 mol, 2% excess). The ESA(aq) was heated to 80 °C and 140 g of ZnO (1.72 mol, 3.44 equiv.) was added over 30 min. The hot solution was allowed to partially cool before being reduced *in vacuo* (3 mmHg) to a solid residue. The product was washed with isopropyl alcohol and ether. The solid product was reduced to constant weight *in vacuo* (1 mmHg). Theoretical yield = 487 g, actual yield = 450 g (92%). For $Zn(O_3SEt)_2$; %Zn/%S (theoretical) = 1.02, %Zn/%S (actual) = 1.04.

Solubility measurements

The saturation aqueous solubility values were determined by measuring the metal content of saturated aqueous solutions using an ICP-emission technique. The experimental method involved cleaning a Kimble glass vial with 1 M HCl(aq) and DI water followed by the transfer of 2–4 g of sample into the clean glass vial and the addition of 2 mL of DI water along with a clean magnetic stir bar. The solution was stirred for 4 h at room temperature and then placed in a temperature controlled oven (22 ± 1 °C) for at least 48 h. During this equilibration period, particulate solids settled out. The saturated solution was removed from the controlled temperature chamber, and, for verification, the solution temperature was checked. The density of the saturated solution was determined by weighing an accurately measured volume of saturated solution. The density determination was repeated at least three times to ensure precision. Next, 0.2 ml of saturated solution was transferred into a volumetric flask and diluted to an appropriate volume. The percentage metal in the original saturated solution was determined *via* the use of a calibration curve developed with accurate standards. The analysis technique used was ICP-AES (inductively coupled plasma-atomic emission spectroscopy), except for the potassium and mercury salts which were analyzed by AA (atomic absorption spectroscopy). The analyses were repeated at least twice to insure precision. The data were compiled, and our results were compared to literature data, where such data were available (*e.g.*, for the sulfate and chloride salts), to ensure that there was no more than 5% relative error.

Conductivity measurements

Standard aqueous acid solutions were made up by adding an appropriate amount of acid to DI water. The concentrations of the various acid solutions were checked by pH titration. Conductivity values were determined using an Orion model 142 conductivity meter.

Electrowinning procedures

The acids and salts were obtained or prepared as described above. The divided cell electrowinning apparatus was designed and produced at Elf Atochem NA. The material presented below is essentially identical to experimental details included in a US patent application (08/798985) and in a presentation delivered to the *12th Annual International Forum on Electrolysis in the Chemical Industry*.[34]

Procedure 1; electrowinning of various metals from an undivided cell

A series of electrowinning experiments were performed in an undivided electrochemical cell charged with 250 ml of an appropriate aqueous solution of a metal alkanesulfonate salt. The cell was fitted with a stainless steel cathode (50 cm^2) and an IrO_2 (30 cm^2) coated titanium inert anode. The average interelectrode spacing was 2 in. A constant current of 3 A (cathode current density = 60 mA cm^{-2}, anode current density = 100 mA cm^{-2}) was passed through the cell until most of the metal was removed and/or a steady-state level of metal concentration was obtained. The solution temperature was not maintained at room temperature, and resistive heating normally raised the temperature of the solution from room temperature to 35 °C during the first hour of the electrolysis. The electrolysis temperature was allowed to stabilize at 35 °C for the remainder of the experiment. The volume of the solution was maintained constant throughout the electrolysis by occasional additions of distilled water. Following the passage of an appropriate amount of charge (calculated as current × time), the solutions were filtered and analyzed for metal and acid content. Representative data are tabulated in Table 5.

Procedure 2; electrowinning of iron from a divided cell

A divided cell electrowinning apparatus (see Fig. 1) was fitted with a stainless steel cathode (55.6 cm^2), an iridium oxide coated titanium mesh anode (33.3 cm^2) and an ESC 7001 anion exchange membrane (111.1 cm^2). The catholyte chamber was charged with 1 L of a 0.47 molar aqueous solution of iron(II)/iron(III) methanesulfonate. The anode chamber was charged with 1 L of 0.1% aqueous solution of methanesulfonic acid (*ca.* 0.01 M). A current of 3 A, at *ca.* 14 V, was passed for 24 h (2.7 Faradays of charge, cathode current density = 54 mA cm^{-2}, anode current density = 90 mA cm^{-2}, membrane current density = 27 mA cm^2). The compositions of the catholyte and anolyte before/after electrolysis are shown in Table 6.

Procedure 3; electrowinning of nickel and acid transport in a divided cell

A divided cell electrowinning apparatus as described in procedure 2 was used for this experiment. The catholyte chamber was charged with 1 L of a spent electroless nickel bath (5 g L^{-1} Ni^{2+}, 40 mL L^{-1} lactic acid, 30 g L^{-1} hypophosphite) in which the pH had been raised from 4.8 to 8.5 with ammonia (color change from green to blue). The anolyte chamber was charged with 1 L of a 1% aqueous solution of methanesulfonic acid (*ca.* 0.1 M). A current of 1 A, at *ca.* 10 V, was passed for 32 h (1.2 Faradays of charge, cathode current density = 18 mA cm^{-2}, anode current density = 30 mA cm^{-2}, membrane current density = 9 mA cm^{-2}). The compositions of the catholyte and anolyte before and after electrolysis are shown in Table 7.

Procedure 4; electrolytic stability of methanesulfonic acid

The robustness of aqueous alkanesulfonic acid electrolytes was assessed by subjecting 10% aqueous solutions of MSA (*ca.* 1 M) to 24 h of electrolysis (production of hydrogen on the cathode, production of oxygen on the anode) at various current densities in an undivided cell. The cathode was a piece of polished silver. The anode was an IrO_2 coated titanium mesh. The increase in the sulfate concentration of MSA solutions following 24 h of electrolysis at various current densities is tabulated in Table 8.

The low levels of sulfate formation, even after 24 h of electrolysis at useful electrowinning current densities, illustrate the robustness of aqueous methanesulfonic acid (MSA) based electrolytes. The small amount of sulfate which did form was produced *via* a poorly characterized anodic oxidation of both MSA and certain low level impurities (*e.g.*, dimethyl sulfone) commonly present in MSA.

Addendum; metal alkanesulfonate preparations

The metal methanesulfonate salts used in this study were produced by employing one of the four general methods discussed below. Note that detailed experimental procedures are given in the Experimental section.

Generically, all simple metal salts are produced by metathesis reactions. Such metatheses can either be between two metal salts (one containing the anion and the other containing the cation sought) or they can be between the acid form of the desired anion and a metal salt containing the desired metal cation. A general depiction of the two processes are represented below in eqns. (10a) and (10b).

$$ML_n + M'X_n \rightarrow M'L_n + MX_n \qquad (10a)$$
$$ML_n + n\,HX \rightarrow MX_n + n\,HL \qquad (10b)$$

For a salt preparation to be successful, either the equilibrium must favor the product or the equilibrium must somehow be shifted toward the product. In addition, for the recovery of a pure salt, the by-product (HL or ML) must be readily separable from the product (MX_n). The equilibria can be shifted toward the product by, for instance, the application of sufficient voltage (electrochemical process), or by the constant removal of the ML_n or HL by-product (chemical process). By-product removal can be accomplished by simple *in vacuo* distillation (*e.g.*, with a volatile acid by-product) or by solubility driven precipitation (*e.g.*, with AgCl or $CaSO_4$ by-product). Even in cases where a zero-valent metal is chemically oxidized to a desired salt, reaction (10b) is applicable, as an intermediate reactant salt will be produced *in situ* by the action of the oxidizing agent on the metal.

Perhaps the most straight-forward method for producing a simple metal salt involves the reaction of equinormal amounts of a basic metal salt with the acid form of the anion of interest (acid plus a base yields a salt). Typical basic metal salts include carbonates, hydroxides and oxides. In this case, the equilibrium lies naturally to the right, and the product is readily isolated by the removal of by-product water *in vacuo*. In our case, we reacted the

Table 5 Experimental data from electrowinning experiments in an undivided cell with metal alkanesulfonates

Metal[a]	[Metal] (initial)[b]/g L^{-1} (M)	[Metal] (final)[c]/g L^{-1} (M)	[Acid] (initial)[d]/ mol kg^{-1}	[Acid] (final)[e]/ mol kg^{-1}	Completion M/A[f] (%)	Current efficiency[g] (%)
Palladium (MS)[h] **19**	4.5 (0.04)	0 (0)	0.03	0.15	100/150	57
Silver (MS) **13**	109 (1.01)	3 (0.03)	0.02	0.97	97/97	53
Copper (PS) **20**	63 (0.99)	0.2 (0.003)	0.01	2.01	99 /106	79
Tin (ES) **21**	59 (0.50)	0.4 (0.003)	0.05	1.01	99/96	85
Lead (MS) **18**	184 (0.89)	0.4 (0.002)	0.01	2.01	100/112	130[i]
Nickel (PS) **22**	51 (0.87)	36 (0.61)	0.02	0.55	29/102	17
Cobalt (ES) **23**	55 (0.93)	40 (0.68)	0.01	0.68	27/134	14
Cadmium (PS) **24**	66 (0.59)	0.1 (0.001)	0.04	1.61	100/133	46
Iron (MS) **25**	54 (0.97)	46 (0.82)	0.02	1.01	15/330	81
Iron/tin[j] (MS)	26 (0.46)	26 (0.46)	0.22	0.36[k]	0/UD[l]	UD[l]
Zinc (PS) **26**	56 (0.86)	18 (0.27)	0.03	1.21	68/100	23
Zinc (ES) **27**[m]	66 (1.01)	5 (0.08)	0.01	1.54	92/82	52

[a] Metals were dissolved in DI H_2O as Pd(II), Ag(I), Cu(II), Sn(II), Pb(II), Ni(II), Co(II), Cd(II), Fe(II)/(III), Zn(II). [b] The initial concentration of the metal before electrowinning expressed as g metal per liter of solution with molarity in parentheses; by ICP/emission analysis. [c] The final concentration of the metal following electrowinning expressed as g metal per liter of solution with molarity in parentheses; by ICP/emission analysis. [d] The initial concentration of strong acid before electrowinning expressed as mol H^+ per kg solution; by pH titration. [e] The final concentration of strong acid after electrowinning expressed as mol H^+ per kg solution; by pH titration. [f] The percentage completion of the process (M/A) based on: M: the amount of metal removed from solution relative to the total amount of metal originally present. A: the amount of acid present in the final solution relative to the total amount possible for the amount of metal removed by electrodeposition. Values of A which are >100% are the result of measurement uncertainties, unknown variables and/or the formation of soluble/suspended high valent metal oxide compounds. High valent metal oxide compounds yield excess acid upon formation, but the metal compounds also continue to remain in solution. The formation of high valent metal oxide compounds results in net acid production without the metal being removed from solution. Values of A which are <100% result from measurement uncertainty. [g] The percentage current efficiency of the process based on the amount of metal removed. The current efficiency was calculated as mn/q (m = mol metal removed, n = metal valence, q = mol equiv. of charge passed). The total charge passed (TCP), in coulombs, can be calculated as [(mol metal removed) × (metal valence) × (1/current efficiency) × 96,487]; the total electrolysis time, in s, can be calculated as TCP/(3), a current of 3 A was used. [h] MS = methanesulfonate, ES = ethanesulfonate, PS = propanesulfonate. [i] A current efficiency of >100% was obtained because lead was being removed at both electrodes. [j] Sample obtained from an operational Fe removal system (analysis = 0.46 M Fe, 0.08 M Sn, 0.22 M MS). [k] This acid was generated by the efficient electrowinning of the small amount of tin which was present in the solution. [l] UD = undefined; acid recovery values and current efficiency relative to the iron concentration are undefined. [m] This experiment employed a special high surface area carbon cathode for the final stages of the electrowinning.

Table 6 The electrowinning of iron from a divided electrowinning cell

Chamber[a]	[Iron] (initial)[b]/g L^{-1} (M)	[Iron] (final)[c]/g L^{-1} (M)	[Acid] (initial)[d]/m	[Acid] (final)[e]/m	Completion[f] (%)	Current efficiency (%)
Catholyte	26.2 (0.47)	0.9 (0.02)	0.02	0.02	96	33[g]
Anolyte	26.0 (0)		0.01	0.88	98	32[h]

[a] The chamber of the divided electrowinning cell. [b] The initial concentration of the metal before electrowinning expressed as g metal per liter of solution with molarity in parentheses; determination by ICP/emission analysis. [c] The final concentration of the metal following electrowinning expressed as g metal per liter of solution with molarity in parentheses; determination by ICP/emission analysis. [d] Initial concentration of strong acid before electrowinning expressed as mol protons per kg solution; by pH titration. [e] Final concentration of strong acid after electrowinning expressed as mol protons per kg solution; by pH titration. [f] Catholyte: the percentage completion based on the amount of metal removed. Anolyte: the percentage completion based on the amount of acid produced relative to the total amount of iron removed. [g] Cathode: the percentage current efficiency based on mol of metal removed per mol of charge passed. The current efficiency was calculated as mn/q (m = mol metal removed, n = metal valence, q = mol equivalents charge passed). [h] Anode: the percentage current efficiency (oxygen evolution with regeneration of acid) was close to 100%; the observed inefficiency (apparent inefficiency) was due to the leakage of protons across the membrane. The percentage current efficiency was calculated as H/q (H = mol of recoverable acid generated, q = mol equivalents of charge passed).

desired alkanesulfonic acid with a commercially available basic metal salt. The preparations of sodium (**3**), lead (**18**) and silver (**13**) methanesulfonate are shown in eqns. (11)–(13).

$$\mathrm{NaOH + MeSO_3H \rightarrow NaO_3SMe + H_2O} \tag{11}$$

$$\mathrm{PbCO_3 + 2\ MeSO_3H \rightarrow Pb(O_3SMe)_2 + H_2O + CO_2} \tag{12}$$

$$\mathrm{Ag_2O + 2\ MeSO_3H \rightarrow 2\ AgO_3SMe + H_2O} \tag{13}$$

A less common method of salt manufacture involves ligand metathesis between an acid and an acidic salt. In this case, the equilibrium does not lie strongly to the right, and the reaction must be driven forward by the continuous removal of at least one reaction product. In our case, we mixed metal nitrates with alkanesulfonic acids, and we drove the reaction to completion by the continuous removal of nitric acid *via* vacuum distillation. This method was used by us in the preparation of silver (**13**) and

Table 7 The electrowinning of nickel in a divided electrowinning cell

Chamber	[Ni] (initial)/g L^{-1} (M)	[Ni] (final)/g L^{-1} (M)	[Acid] (initial)/ mmol g^{-1}	[Acid] (final)/ mmol g^{-1}
Catholyte	5 (0.08)	0	1.38	0
Anolyte	0	0	0.13	1.67[a]

[a] Acid concentrations in mmol protons per g solution. The 1.67 m acid in the anolyte at the end of the electrowinning experiment was composed of 9% acetic acid, 65% methanesulfonic acid and 26% lactic acid.

Table 8 The formation of sulfate from methanesulfonate under electrolysis conditions similar to those useful for electrowinning

Current density/mA cm^{-2}	Sulfate concentration (ppm)
Cathode = 32 mA cm^{-2}, anode = 20 mA cm^{-2}	12
Cathode = 64 mA cm^{-2}, anode = 40 mA cm^{-2}	12
Cathode = 96 mA cm^{-2}, anode = 60 mA cm^{-2}	14

mercury(II) (**17**) methanesulfonate, as shown in eqns. (14) and (15). It is interesting that the mercury(II) salts of methanesulfonic, ethanesulfonic and propanesulfonic acids were unusually unstable. In all three cases, we had trouble making these mercury(II) salts by simple acidification of mercuric oxide. The nitrate metathesis reaction provided us with a convenient method for making small amounts of these mercury(II) alkanesulfonate salts.

$$AgNO_3 + MeSO_3H \longrightarrow AgO_3Me + HNO_3\ (g)\uparrow \qquad (14)$$

$$Hg(NO_3)_2 + 2\ MeSO_3H \longrightarrow Hg(O_3SMe)_2 + HNO_3\ (g)\uparrow \qquad (15)$$

Another common method for the preparation of salts involves chemical or anodic oxidation of the metal of interest in an electrolyte containing the acid form of the desired anion. For chemical oxidation, this type of reaction can be thought of as *in situ* formation of a nascent metal oxide followed by acidification. Methods of this type generally avoid the problems associated with the sluggish reaction of passive metal oxides. Many metal oxides dehydrate and become somewhat passivated on standing (*e.g.*, precious metal oxides), and it is sometimes more convenient to react such oxides immediately as they are formed.

For anodic oxidation of a metal in an acid medium, the process can be viewed most simply as the direct introduction of the metal cation into the solution. Anodic (electrochemical) oxidation methods for the production of a metal salt require a method for preventing the metal cation of the salt from redepositing on the cathode. In general, divided electrochemical cells are employed for this purpose. The cells can be divided by simple micropore frits or, more desirably, by anion-exchange membranes. We developed chemical oxidations for the production of silver (**13**) and palladium (**19**) methanesulfonate, as shown in eqns. (16) and (17). We also developed an anodic oxidation for the production of silver methanesulfonate **13**, as shown in eqn. (18).

$$2\ Ag + H_2O_2 + 2\ MeSO_3H \longrightarrow 2\ AgO_3SMe + 2\ H_2O \qquad (16)$$

$$2\ Pd + 2\ HNO_3 + 4\ MeSO_3H \longrightarrow 2\ Pd(O_3SMe)_2 + 2\ NO + 12\ O_2 + 3\ H_2O \qquad (17)$$

$$Ag \longrightarrow Ag^+\ (anode) + e^-\ MeSO_3H + e^- \longrightarrow 12\ H_2\ (g) + MeSO_3^-\ (cathode) \qquad (18)$$

It should be noted that silver methanesulfonate is a useful intermediate for the preparation of other metal methanesulfonate salts *via* AgCl precipitation driven reactions with appropriate metal chlorides. The basic reaction is shown below, for the preparation of tin(II) methanesulfonate, in eqn. (19).[35] The preparation of tin(II) methanesulfonate is hindered by the tendency for Sn(II) to oxidize to Sn(IV), and the use of AgO_3SMe is sometimes most convenient for laboratory scale preparations.

$$SnCl_2 + 2\ AgO_3SMe \longrightarrow Sn(O_3SMe)_2 + AgCl(s) \qquad (19)$$

A conceptually simple method for the production of metal salts involves simple acidic leaching of the desired metal. This reaction can be viewed as simple oxidation of the metal by protons. As such, this is the only method which does not formally involve any sort of cation/anion metathesis reaction, and this type of process, when possible, is the most simple. Such processes are commonly used in the recycle loops of zinc electroplating lines which employ inert anodes. The inert anodes for this application are designed to convert water into oxygen and acid. Inert, or insoluble, anodes are to be contrasted with soluble anodes which directly replace by oxidative dissolution the metal cation being electroplated out of the solution. Inert anodes are used despite the inconvenience they introduce, because they allow for a very exact inter-electrode spacing to be maintained. The use of oxygen generating inert anodes in a zinc electroplating system results in a steady increase in the acidity of and a decrease in the metal content of the electroplating solution. To balance the acidification caused by the use of such inert anodes in a zinc plating process, a portion of the operating plating solution is continually passed over zinc granules. The zinc granules react with the excess acid to yield a replenishing zinc salt. It is worth noting that care must be taken to insure that the hydrogen gas formed by this process is properly vented. In our case, we used acidic leaching for the production of iron(II) methanesulfonate **25** as shown in eqn. (20).

$$Fe + 2\ MeSO_3H \longrightarrow Fe(O_3SMe)_2 + 12\ H_2 \qquad (20)$$

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Paper 9/00157C

Microwave-assisted eco-friendly synthesis

of 2-alkylated hydroquinones in dry media†

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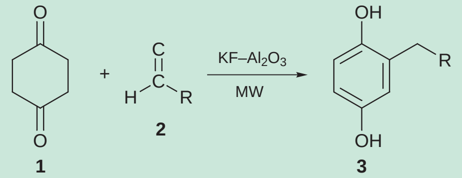
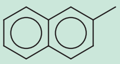
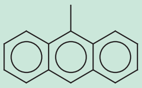
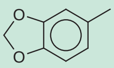
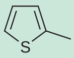
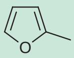
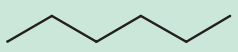
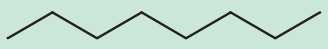
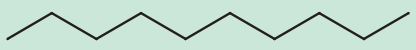
Summary

An environmentally benign process for the synthesis of 2-alkylated hydroquinones under microwave irradiation using 1,4-cyclohexadione and aldehydes catalysed by KF–Al_2O_3 in dry media is reported.

Table 1 Microwave assisted preparation of 2-alkylated hydroquinones



Entry	R	Irradiation time/min	Yield of **3** (%)
a	Ph	3	85
b	p-$MeOC_6H_4$	3	90
c	p-MeC_6H_4	3	95
d	p-BrC_6H_4	4	85
e	p-$O_2NC_6H_4$	5	75
f	p-ClC_6H_4	4	82
g		4	80
h		5	78
i		3	87
j		2	90
k		2	88
l		2	75
m		2	77
n		2	80

Introduction

2-Alkylated hydroquinones are versatile chemicals with wide application in synthesis and industry[1] and efforts towards the synthesis of these compounds involve C–C bond forming reactions starting from hydroquinones or quinones. However, harsh reaction conditions limit the use of these methods with regard to the nature of the side chain requirements on the hydroquinone. An attractive approach for the synthesis of 2-alkylated hydroquinones has been reported[2] recently, which involves heating of cyclohexa-1,4-dione and aldehydes with lithium or magnesiumhalides as catalysts in solvents such as DMI (*N*,*N′*-dimethylimidazolidinone), pyridine, HMPA, DMF, TMEDA, DMPU (*N*,*N′*-dimethylpropyl urea), *etc.* Surface mediated solid phase reactions involving inorganic solids are becoming increasingly important and condensation of a variety of active methylene and carbonyl compounds has been reported both under conventional and microwave heating.[3] In this context, we report here a convenient method for the synthesis of 2-alkylated hydroquinones catalyzed by KF–Al_2O_3 under microwave irradiation.

Results and discussion

Thus several aldehydes undergo condensation with 1,4-cyclohexadione when subjected to microwave irradiation in the presence of KF–Al_2O_3[4] in dry media. From the results summerized in Table 1 the generality of the reaction is evident, as a variety of aromatic, aliphatic, and heterocyclic aldehydes react to form 2-alkylated hydroquinones in good yields (75–95%) within a very short time of irradiation (2–5 min). The conversions are fairly clean, free from aromatic by-products and, unlike conventional approaches for the synthesis of these compounds which involve

Green Context

Substituted hydroquinones are important intermediates for a variety of end-products. Their properties can be tuned for a particular application by variation of the substituent(s). Existing processes for the preparation of these compounds often involve severe conditions and environmentally unfavourable solvents. The use of a solid base and microwave activation has led to a quite general and simple route to these materials with good selectivity and yield. While the general isolation procedure here is unlikely to be applicable on a larger scale, the development of appropriate isolation procedures on a case-by-case basis will make this an attractive process. Similarly, the ability to recycle the solid base will further improve the method. ***DJM***

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† IICT Communication No. 4240.

heating (150–160 °C) in expensive and often hazardous solvents, our method under microwave irradiation occurs at a much lower temperature range (100–110 °C, highest observed temperature after irradiation) in the absence of such solvents. Also, unlike the conventional approach for this transformation which involves aqueous work-up generating high volumes of toxic effluents, our method is almost effluent free and safe.

In conclusion we have demonstrated a quick and convenient method for the high yield preparation of 2-alkylated hydroquinones, using the inexpensive surface bound reagent KF–Al_2O_3 under solvent free conditions and employing microwave irradiation techniques, which may find applications in organic synthesis.

Experimental

In a typical procedure a mixture of benzaldehyde (1.6 g, 10 mmol), cyclohexa-1,4-dione (1.12 g, 10 mmol) and 37% w/w KF–Al_2O_3 (3 wt. equiv. of aldehyde) was placed in a Pyrex test tube and subjected to microwave irradiation at an output of 600 W. After completion of the reaction (3 min) as indicated by TLC, the reaction mass was cooled to room temperature, directly charged on a silica gel column (100–200 mesh) and eluted (ethyl acetate–hexane, 3:7) to afford 2-benzylhydroquinone as a white crystalline solid (1.7 g, 85%), ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 2H), 6.4–6.6 (m, 3H), 7.1–7.3 (m, 5H), 8.2 (br s, 2H).

Acknowledgement

B. V. S. thanks CSIR, New Delhi for a fellowship award.

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Bioconversion of toluene to *p*-hydroxybenzoate

via the construction and characterization of a recombinant *Pseudomonas putida*

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Summary

Biocatalytic production of *p*-hydroxybenzoate (HBA) provides improved regiospecificity over Kolbe–Schmitt carboxylation of phenol while achieving significant source reductions in the generation of waste and byproducts. Construction of the organism for HBA production was accomplished through two classical approaches for the engineering of organisms in the production of specialty chemicals: (1) strain enhancement through chemical mutagenesis to create a mutant *Pseudomonas putida*, EM2839, deficient in HBA degradation, and (2) hybrid pathway construction through the recruitment of genes encoding the toluene-4-monooxygenase (T4MO) (*tmoABCDE*), *p*-cresol methylhydroxylase (*pchCF*), and *p*-hydroxybenzaldehyde dehydrogenase (*phbz*) genes from existing pathways and stably incorporating them into the organism through the use of mini-Tn*5* transposon systems.

Time course measurements of HBA production by resting cells of *P. putida* EM2878 in batch cultures revealed that T4MO conversion of toluene to *p*-cresol, the first step in the pathway, significantly constrained the carbon flux in the pathway, yielding a maximum rate of HBA production of 1.61 ± 0.15 nmol $\mathrm{min^{-1}}$ mg $\mathrm{protein^{-1}}$. In fed-batch culture, toluene conversion to HBA by *P. putida* EM2878 showed absolute selectivity for *para*-hydroxybenzoate production. Maximum HBA concentrations of 35 mg $\mathrm{l^{-1}}$ were achieved in about 28 hours of operation. However, the rate of HBA production was significantly less than that observed during batch studies. The slower rate of HBA production observed in the fed-batch culture was correlated with the degradation of specific T4MO polypeptides.

Introduction

Hydroxybenzoate synthesis constitutes a 7000 ton per annum industry. It is used primarily as a chemical intermediate in the production of liquid crystal polymers, and in the manufacturing of dyes, pesticides, pharmaceuticals, and preservatives. Industrial synthesis of HBA proceeds almost solely by the Kolbe–Schmitt carboxylation of phenol. The process is both energy intensive, requiring successive reactor cycle operations at 220 °C and 0.45 MPa, and lacks absolute regiospecificity. Only 48% of the available potassium phenolate is converted to HBA. The reactive nature of the phenolic oxygen results in the loss of 12% of the available starting material to dead-end waste byproducts.[1] The remaining potassium phenolate (40%) is oxidized back to phenol, a United States Environmental Protection Agency (EPA) priority pollutant under the Clean Air and Water Act, which must be recovered from waste gas and water streams.[2] Other process emissions include metal salts and heavy residues (tar) which are becoming increasingly expensive to landfill and incinerate, and CO_2 gas emissions, the principal cause of global warming.[3] In view of the growing emphasis placed on environmentally benign synthesis strategies, alternatives to the current technology yielding higher selectivity and minimizing waste generation are being sought.

Industrial interest in the enzymes of the aromatic catabolic pathways has focused on the regio- and stereo-selective nature with which mono- and di-oxygenases can incorporate molecular O_2 directly into the aromatic ring. The efficiency and selectivity with which these enzymatic reactions can be conducted is unmatched using traditional chemistry. Examples include the use of the toluene dioxygenase of *Pseudomonas putida* F1 in the production of *cis*-dihydrodiols and catechol,[4] and the biological production of indigo, which relies on the action of the naphthalene dioxygenase from *P. putida* PpG7 to form indoxyl, an intermediate which spontaneously condenses to form indigo upon exposure to air.[5,6] Furthermore, the study of the microbial degradation of environmental pollutants has stimulated the rational design of biosynthetic routes for production of specialty chemicals using engineered organisms.

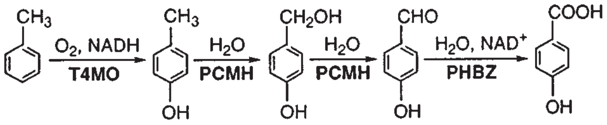
Green Context

Biocatalysis represents a potentially powerful clean route to many complex chemicals. However, finding the right microorganism is not always easy. This paper describes the development of a strain of organism capable of the clean and selective production of *para*-hydroxybenzoate from toluene, a one step process without parallel in classical organic chemistry. The new process generates less waste than the classical route (which proceeds *via* phenol).

One of the (almost) generic weaknesses in such an approach is the lower solution concentrations of product compared to the alternative chemical route(s). However, the use of water as the reaction medium avoids the use of organic solvents. Isolation is therefore often energy intensive, but constant progress in separation technology makes this biotechnological approach increasingly valid.

DJM

The goal of this research is to explore the potential of using biocatalysis as a cleaner and simpler alternative to the traditional Kolbe–Schmitt synthesis of HBA. As a model biosynthetic process, we chose to study the bioconversion of toluene to HBA using a single recombinant organism. Central to the conversion of toluene to HBA in *P. putida* EM2878 is the T4MO system from *P. mendocina* KR1. T4MO, a 4-component monooxygenase, catalyzes the conversion of toluene to *p*-cresol by regioselective incorporation of 1 atom of O_2 into the aromatic ring.[7,8] Transformation of *p*-cresol to *p*-hydroxybenzaldehyde is catalyzed by *p*-cresol methylhydroxylase (PCMH), a cytochrome c:flavoprotein from *P. putida* NCIB9869 that incorporates the oxygen from water into the methyl group of *p*-cresol to give *p*-hydroxybenzyl alcohol, followed by dehydrogenation to give *p*-hydroxybenzaldehyde.[9] The final step, dehydrogenation of *p*-hydroxybenzaldehyde to HBA, is catalyzed by PHBZ, an NAD^+ dependent aromatic aldehyde dehydrogenase from *P. putida* NCIB9866.[10] The reaction sequence is given in Fig. 1.



1 2 3 4 5

Fig. 1 Pathway for the bioconversion of toluene to HBA. **1**, toluene; **2**, *p*-cresol; **3**, *p*-hydroxybenzyl alcohol; **4**, *p*-hydroxybenzaldehyde; **5**, HBA.

In this paper we describe the initial construction of a recombinant microorganism, *P. putida* EM2878, which overexpresses genes obtained from the aforementioned *Pseudomonas* sp. for the bioconversion of toluene to HBA. Bottlenecks to carbon flux through the pathway are identified, and dependence of HBA production on toluene and salicylate induction of T4MO are quantified. In addition, ultimate HBA concentrations obtained in fed-batch studies are reported with productivity being compared to that obtained in batch culture studies.

Results

Recombinant system construction

Initial studies of PobA activity in *P. putida* KT2440 revealed that HBA turnover was rapid in the presence of various primary carbon sources. In order to effect HBA accumulation from toluene it was necessary to disrupt PobA, the enzyme catalyzing the *m*-hydroxylation of HBA to protocatechuate in the protocatechuate branch of the β-ketoadipate pathway.[11] Following nitrosoguanidine mutagenesis and 3 rounds of (+)-cycloserine–piperacillin enrichment, approximately 3000 colonies were screened for loss of PobA activity. 195 colonies were intially isolated that showed no growth on solid HBA minimal media and positive growth on benzoate minimal media. Of these, 4 colonies were shown to be deficient in PobA activity following activity assay of crude extracts. Both HBA and *p*-hydroxybenzaldehyde were used as inducers to distinguish between loss of PobA activity and loss of the HBA transport system;[12] Table 1. One Pob^- mutant from the original 4 was selected at random to be the host of the system and was designated *P. putida* EM2839.

Construction of pESM21 and pESM23 allowed for the independent regulation of T4MO from PCMH and PHBZ through the use of independent *Psal* and *Ptrc* promoters, respectively. Partial restriction maps of the resulting transposon configuration are shown in Fig. 2. Mating of *E. coli* S17-1λpir/pESM23 with *P. putida* EM2839 afforded the intermediate construction of *P. putida* EM2840, which contains both *pchCF* and *phbz* genes under *Ptrc* control and kanamycin selection. The addition of the T4MO genes was obtained through a second mating of *P. putida* EM2840 with *E. coli* S17-1λpir/pESM21 giving *P. putida* EM2878.

Table 1 PobA enzyme activity

Strain	Inducer	Specific activity/ μmol min^{-1} mg $protein^{-1}$
P. putida KT2440	10 mM HBA	0.294 ± 0.054
	1.5 mM phbz[a]	0.046 ± 0.011
P. putida EM2839	10 mM HBA	ND[b]
	1.5 mM phbz	ND

[a] *p*-Hydroxybenzaldehyde. [b] None detected.

In addition to the copy of *phbz* placed on the chromosome through transposon insertion of the mini-Tn*5* element of pESM23, *P. putida* EM2878 maintains at least two other copies of *p*-hydroxybenzaldehyde dehydrogenase on the chromosome. One copy of *p*-hydroxybenzaldehyde dehydrogenase exists as part of the *p*-hydroxymandelic acid pathway and is inducible only by *p*-hydroxymandelic acid and *p*-hydroxybenzylformate.[14] The second copy of *p*-hydroxybenzaldehyde dehydrogenase exists independently of the *p*-hydroxymandelic acid pathway and is inducible by *p*-hydroxybenzaldehyde. The addition of *phbz* into the toluene conversion pathway under gratuitous induction minimized possible selection of revertants able to grow on HBA caused by *p*-hydroxybenzaldehyde induction of chromosomal *p*-hydroxybenzaldehyde dehydrogenase.

Toluene conversion to HBA by resting cells of *P. putida* EM2878

Analysis of the pathway revealed two bottlenecks to carbon flux that limited toluene bioconversion to HBA in *P. putida* EM2878. The first is a low level of T4MO activity that results in a slow turnover of toluene to *p*-cresol. This was shown by spiking identical cultures of resting cells of *P. putida* EM2878 with varying levels of *p*-cresol during toluene bioconversion. The HBA profiles generated during this experiment are shown in Fig. 3(a). Upon addition of *p*-cresol, an increase in the rate of HBA production results, apparently due to excess enzyme activity in the lower pathway. The maximum HBA production rate from toluene was measured to be 1.61 ± 0.15 nmol min^{-1} mg $protein^{-1}$, and was independent of whether expression of *tmoABCDE* was from the *Psal* or *Ptrc* promoters (data not shown).

Conversion of *p*-cresol to HBA resulted in higher rates of HBA production than from toluene. However, at higher rates of *p*-cresol turnover, PCMH-catalyzed conversion of *p*-hydroxybenzyl alcohol to *p*-hydroxybenzaldehyde is competitively inhibited by *p*-cresol, creating a second bottleneck in the pathway. The specificity of PCMH for *p*-cresol ($K_m = 16$ μM) is greater than *p*-hydroxybenzyl alcohol ($K_m = 27$ μM)[15] which gives rise to a transient accumulation of *p*-hydroxybenzyl alcohol during *p*-cresol bioconversion to HBA. This can be seen in the concentration profiles in Fig. 3(b) for the batch conversion of *p*-cresol to HBA by resting cells of *P. putida* EM2878. In these experiments HBA production from *p*-cresol was nonlinear with a maximum rate of 17 ± 0.75 nmol min^{-1} mg $protein^{-1}$ while *p*-cresol disappearance was measured to be 26 ± 5.1 nmol min^{-1} mg $protein^{-1}$. Comparison of HBA production rates from toluene and *p*-cresol conversion reveals that HBA production from *p*-cresol proceeds by at least an order of magnitude faster than from toluene.

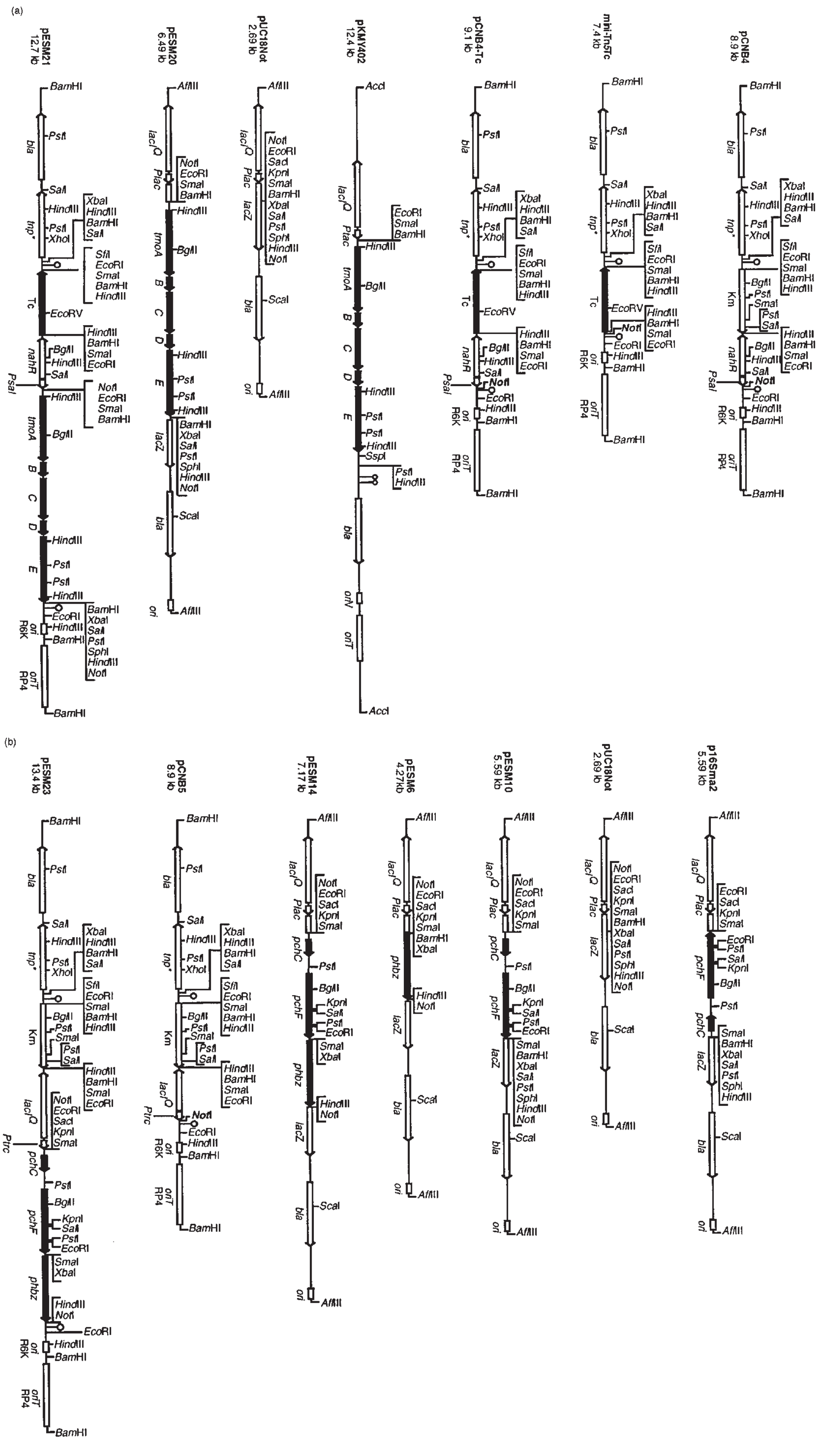


Fig. 2 Partial restriction maps of the plasmids used to create the mobile expression systems (a) pESM21 and (b) pESM23. Arrows indicate the orientation of gene transcription. Filled arrows indicate genes involved in the construction of the target systems. ⫯ indicates the I and O ends of Tn5. ⫯⫯ indicates the strong transcription terminators of *rrnB* locus. The DNA sequences coding antibiotic resistance markers *aphA and tet*, regulatory proteins *lacI*^{Q} and *nahR*, and promoters *Ptrc* and *Psal* are indicated. The mobile units are present in the delivery plasmid pUT as *Xba*I-*Eco*RI restriction fragments.[13]

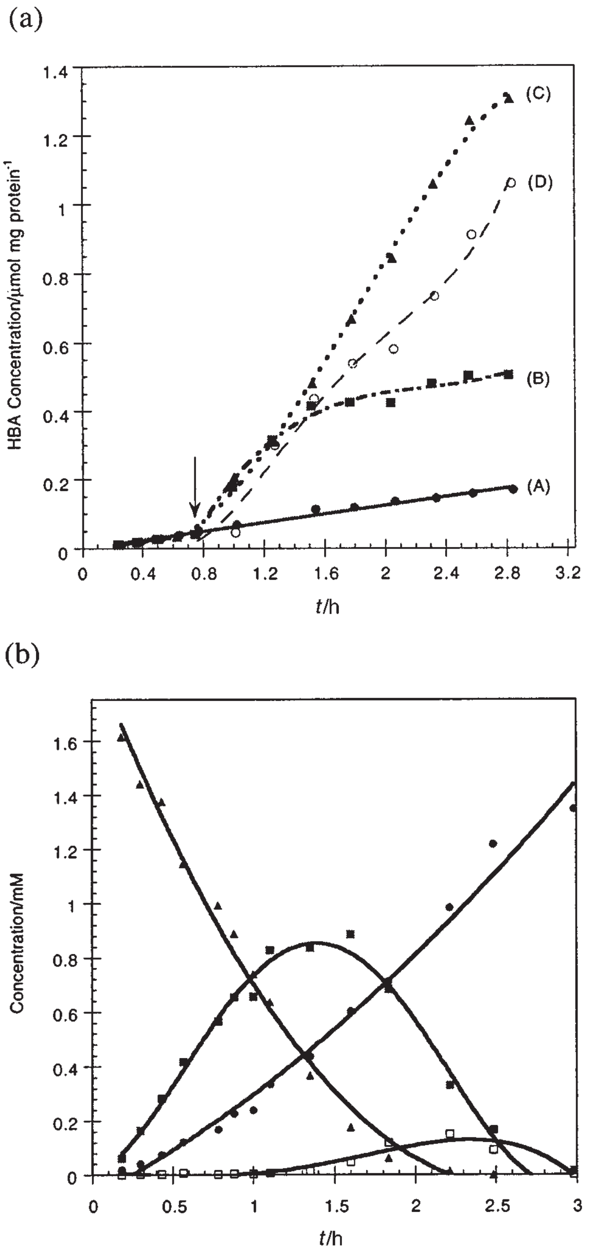


Fig. 3 Determination of carbon flux bottlenecks in toluene bioconversion pathway using resting cells of *P. putida* EM2878. (a) Identification of T4MO rate limiting step. Arrow denotes time at which *p*-cresol was added to culture. Curves indicate amount of *p*-cresol added: (A) 0 ppm; (B) 10 ppm; (C) 50 ppm; (D) 150 ppm. (b) Transient accumulation of *p*-hydroxybenzyl alcohol in conversion of *p*-cresol to HBA. (▲) *p*-cresol; (●) HBA; (□) *p*-hydroxybenzaldehyde; (■) *p*-hydroxybenzyl alcohol. Lines drawn to indicate trends.

Because of the large difference in activities between the upper and lower pathways, the transient accumulation of *p*-hydroxybenzyl alcohol is never observed during toluene conversion to HBA since *p*-cresol cannot be supplied at a high rate by T4MO conversion of toluene. As such, HBA production from toluene is dependent on the level of T4MO induction and toluene concentration.

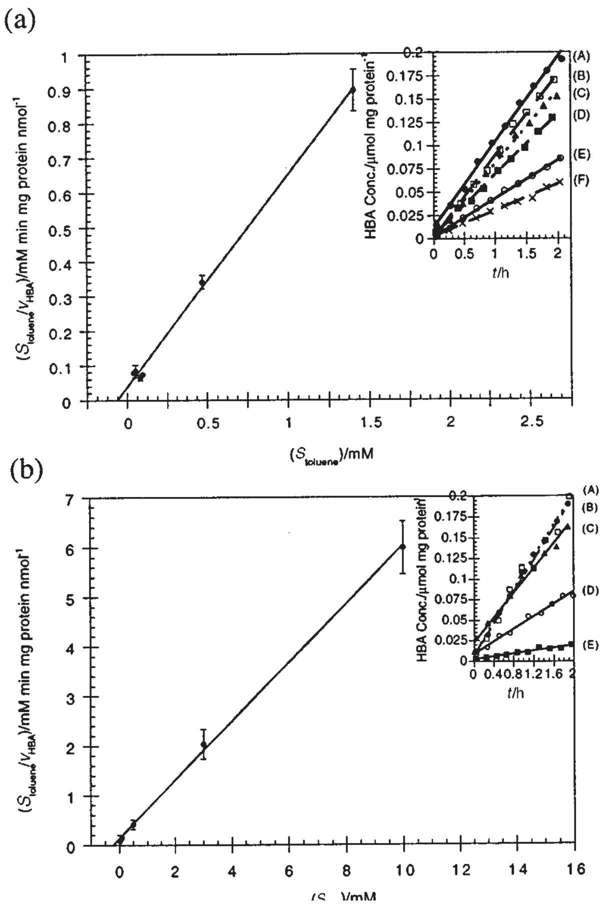


Fig. 4 Instrinsic kinetic parameters for HBA production from toluene by resting cells of *P. putida* EM2878 in batch culture. (a) HBA production dependence on toluene. Inset contains HBA profiles generated at initial toluene concentrations: (A) 1.41 mM; (B) 0.47 mM; (C) 0.094 mM; (D) 0.075 mM; (E) 0.051 mM; (F) 0.039 mM. (b) HBA production dependence on salicylate induction of T4MO. Inset contains HBA profiles generated at salicylate concentrations: (A) 10.0 mM; (B) 3.0 mM; (C) 0.5 mM; (D) 0.1 mM; (E) 0.025 mM.

To qualify this dependence, we determined the intrinsic kinetic parameters characterizing this strain using resting cell suspensions in shake flask studies. The inset of Fig. 4(a) shows the HBA concentration profiles generated at the given initial toluene concentrations. Hanes regression of the data yielded Monod saturation dependence of HBA production on toluene, giving V_{max} = 1.61 ± 0.15 nmol min^{-1} mg protein^{-1} and K_m = 58 ± 5 μM. Fig. 4(b) shows the HBA production dependence on the level of T4MO induction. The inset of Fig. 4(b) shows the HBA profiles generated at the given initial salicylate concentrations. Hanes regresssion of the data yielded V_{max} = 1.69 ± 0.09 nmol min^{-1} mg protein^{-1} and K_m = 208 ± 29 μM. The maximum yield of HBA realized in these studies, 11 to 15 mg l^{-1}, was achieved in about 4 hours.

Toluene conversion to HBA by fed-batch cultures of *P. putida* EM2878

The selectivity of toluene bioconversion to HBA by fed-batch cultures of *P. putida* EM2878 was 99+% for *para*-hydroxybenzoate product. We were unable to detect the presence of *m*-cresol, a possible byproduct of the reaction, by HPLC analysis of culture supernatants (Fig. 5). This peak would appear at 16.67 min in the spectra in Fig. 5, which represents a sample taken after 28 hours of operation. We attribute the high degree of selectivity to the absolute structural requirement by PCMH for a 1–4 juxtaposition of methyl group to hydroxyl group for activity, and 94% selectivity

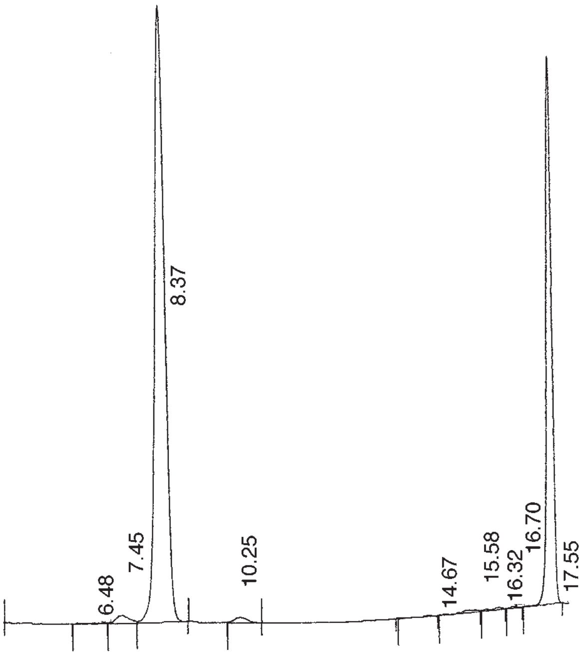


Fig. 5 HPLC spectra of fed-batch supernatant at 28 hours of operation. HBA retention time, 8.37 min; salicylate retention time, 17.55 min; and *m*-cresol retention time, 16.78 min. Compounds at retention times 7.45 and 10.25 min are associated with cellular metabolism of glutamate.

of toluene to *p*-cresol conversion by T4MO reported by several groups.[8,16]

Analysis of fed-batch data in Fig. 6(a) shows that HBA production levels off after approximately 20 hours of operation, reaching a maximum concentration of 34 mg l^{-1}, although the toluene concentration in the reactor is maintained at around 159 ppmm throughout the entire fermentation (Fig. 7(a)). The experimentally determined HBA concentration is roughly 5-fold lower than the 150 mg l^{-1} concentration we would calculate (Fig. 6(b)) assuming that fed-batch HBA production follows the batch HBA production kinetics determined from the Hanes regression of initial rate data presented in Fig. 4. From the rest of the fed-batch data shown in Fig. 7(b) it can be observed that the viable cell population remains constant at about 7.5×10^8 CFU ml^{-1} after 10 hours following an initial 40% reduction in the total viable cell counts. Further comparison of differential cell counts (Fig. 7(b)) reveals that the transposon systems appear to remain stable during the 30 hour duration of the experiment and that the reversion rate of the PobA-blocked mutants appears to be low. From these indicators, we should observe a higher level of HBA production than what is measured. Furthermore, we did not observe the accumulation of any of the downstream intermediates following T4MO catalyzed coversion of toluene to *p*-cresol, suggesting that T4MO activity remained the rate limiting step in toluene conversion to HBA.

The observed discrepancy between batch and fed-batch HBA production could not be described by simple measurement of global variables. The possibility of HBA feed back inhibition of T4MO was explored in shake flask studies. Resting cell experiments were performed as described previously, except that 1 mM HBA was present during the time of induction and measurement of toluene turnover to *p*-cresol by T4MO. This represents a four-fold increase in HBA concentration over what was observed in the fed-batch studies. HBA production rates of 1.58 ± 0.21 nmol min^{-1} mg $protein^{-1}$ were observed, suggesting that feed back inhibition was not the cause of the observed low productivity.

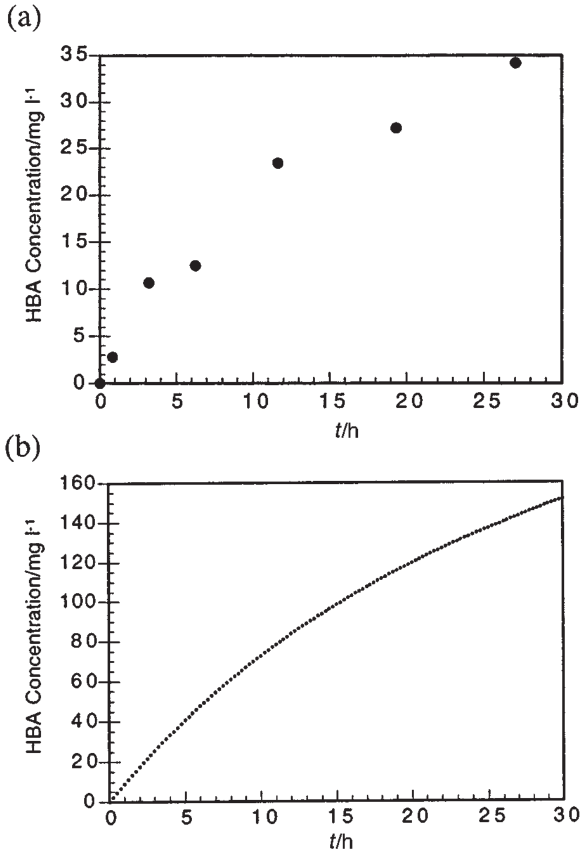


Fig. 6 HBA production by fed-batch culture of *P. putida* EM2878. (a) Experimental data. (b) Calculated HBA concentration based on intrinsic kinetic parameters determined in batch studies.

Since we could not explain that discrepency between batch and fed-batch HBA production by feed back inhibition, we reasoned that the observed low level of HBA production in the fed-batch culture was caused by changes in the level of T4MO enzyme being produced. To test this hypothesis we then measured the relative levels of specific T4MO polypeptides as a function of time during the fed-batch experiment. Fig. 8 and Table 2 summarize the results of densitometric analysis of SDS PAGE separation of total soluble protein samples taken at various time points during the fed-batch experiment. Within the first 10 hours, 81% to 99% of the initial levels of TmoA and TmoE polypeptides are present in the cells. This could be correlated with the high initial activity of toluene to HBA conversion which we observed during the fed-batch experiment. After 10 hours, a reduction in the amount of T4MO protein monomer can be seen, leading ultimately to a 50% decrease from the initial TmoA and TmoE levels at 24 hours. Although this analysis represents an indirect measure of active T4MO protein, the observed decrease in T4MO monomer content qualitatively explains the decreasing rate of toluene conversion to HBA.

Discussion

From the data shown in Fig. 3(a), it is apparent that the rate of toluene conversion to HBA in our strain is controlled by the level of T4MO activity. The maximum rate of HBA production from toluene, 1.61 ± 0.15 nmol min^{-1} mg $protein^{-1}$, is an order of magnitude less than the maximum rate of HBA production from

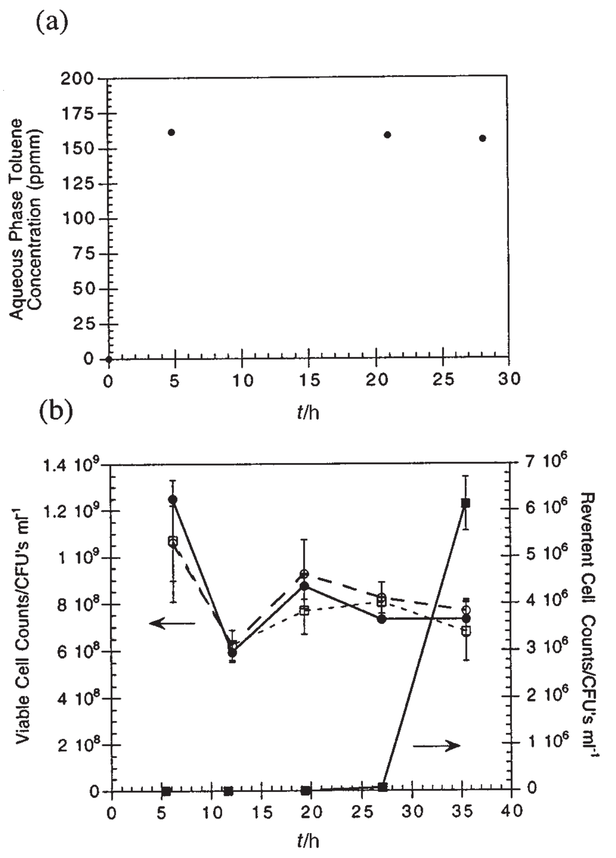


Fig. 7 Global parameters measured during fed-batch operation of toluene bioconversion to HBA by *P. putida* EM2878. (a) Liquid phase toluene concentration. (b) Viable cell counts. (□) tetracycline selection; (○) kanamycin selection; (●) no selection pressure; (■) revertent cell count.

p-cresol for all levels of T4MO induction. Furthermore, *P. putida* EM2871, containing only *tmoABCDE*, showed maximum production rates of *p*-cresol from toluene of 1.62 ± 0.18 nmol min^{-1} mg protein^{-1}, confirming toluene conversion to *p*-cresol as the rate limiting step in the pathway.

Using HBA production as an indirect measure of T4MO activity, our strain is approximately 3-fold less active than strains in which *tmoABCDE* is expressed from broad-host-range expression plasmids employing similar promoter/host configurations.[17] This suggests that transcriptional and translational capacities exist beyond what is being utilized by our monocopy construct. In addition, our construct contains only the 5 essential structural genes, *tmoABCDE*, necessary for functional T4MO activity. These genes encode for the terminal hydroxylase, *tmoABE*, a ferredoxin protein, *tmoC*, and a possible regulatory protein, *tmoD*.[7] A sixth gene not present in our construct, *tmoF*, encodes for an oxidoreductase whose activity can be substituted with a non-specific oxidoreductase produced by *Pseudomonas* sp. and *E. coli*.[17] However, coexpression of *tmoF* with the 5 gene cluster provides a four-fold improvement in activity over expression of the five gene cluster alone.[17] One can surmise that a 10-fold improvement in HBA production from toluene could be realized through coexpression of *tmoF* with *tmoABCDE* and by increasing the copy number of the T4MO cassette through the use of stabilized broad-host-range plasmids. Such an improvement in activity would raise the level of T4MO activity to the same order of magnitude as indirectly observed for PCMH and PHBZ cat-

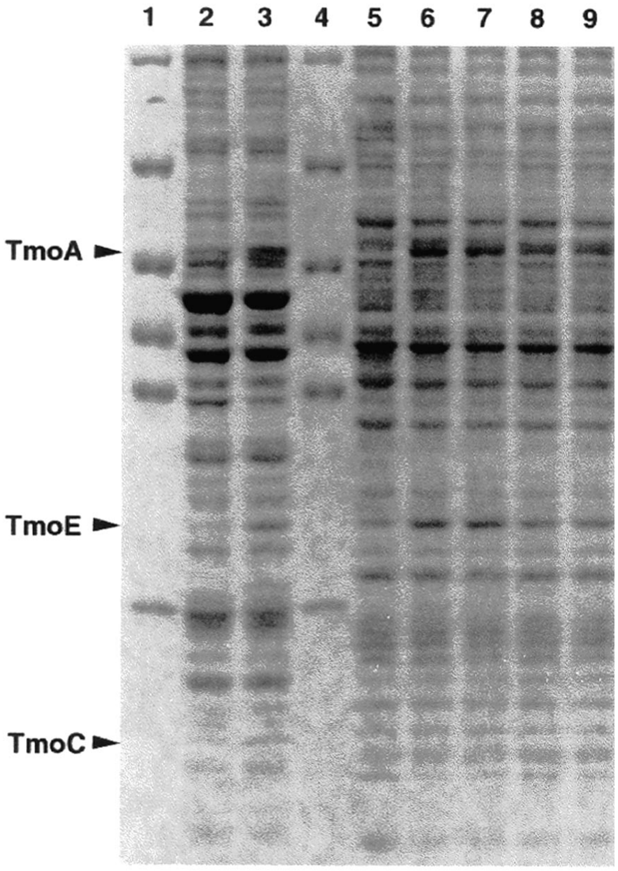


Fig. 8 SDS PAGE analysis of selected T4MO polypeptides as a function of time during fed-batch operation. Lanes 1,4: molecular weight markers. Lane 2: *E. coli* pUC18 induced with 2 mM IPTG; negative control. Lane 3: *E coli* pUC18 with *Eco*RI/*Ssp*I fragment containing *tmoABCDE* genes induced with 2 mM IPTG; positive control. Lanes 5–9 are from various time points during fed-batch operation. Lane 5: uninduced *P. putida* EM2878. Lane 6: steady state induction of T4MO at *t* = 0. Lane 7: *t* = 10.5 h. Lane 8: *t* = 24.1 h. Lane 9: *t* = 29.5 h.

Table 2 Relative intensity of selected T4MO polypeptides as a function of time during fed-batch operation

Lane number	Fed batch time point	TmoA relative intensity[a] (%)	TmoE relative intensity[a] (%)
5	Uninduced[b]	48.4 ± 4.0 (0)[c]	47.3 ± 3.4 (0)
6	*t* = 0	100 (100)	100 (100)
7	*t* = 10.5 h	90.8 ± 1.9 (81.9 ± 5.1)	99.6 ± 0.4 (99.4 ± 0.7)
8	*t* = 24.1 h	72.4 ± 2.6 (46.0 ± 9.3)	74.7 ± 0.9 (52.0 ± 1.4)
9	*t* = 29.5 h	70.3 ± 1.8 (42.1 ± 8.0)	72.8 ± 4.3 (48.7 ± 4.8)

[a] The relative intensity is scaled to the maximum amount of protein observed at *t* = 0. Intensity values represent the fraction of protein remaining using *t* = 0 as a reference point. [b] The background intensities of the uninduced bands are attributed to the presence of co-migrating protein bands. [c] Values obtained by subtracting the intensity of the co-migrating protein bands seen in the uninduced control.

alyzed conversion of *p*-cresol to HBA. This could potentially shift the carbon flux bottleneck from T4MO catalyzed conversion of toluene to *p*-cresol, to PCMH catalyzed conversion of *p*-hydroxybenzyl alcohol to *p*-hydroxybenzaldehyde. This would be indicated by the appearance of *p*-hydroxybenzyl alcohol as a transient intermediate during the conversion of toluene to HBA.

In addition to further improvements in T4MO activity, more work is necessary to determine the mechanism responsible for the degradation of T4MO monomers seen in the fed-batch study. At present we can correlate the decreased level of productivity in the fed-batch culture with the reduction of specific T4MO polypeptides. One or more of the following mechanisms can be speculated to be at work; increased protein turnover due to the scarce availability of a primary carbon source for growth;[18] inability of the host to fully supply the necessary oxidoreductase component of T4MO resulting in incomplete processing of T4MO subunits into active protein, which leads to its degradation by protease activity found in the cytoplasm;[18] increased proteolytic activity due to a cell specific response to increased internal levels of HBA. We have begun work aimed at understanding this phenomenon and are exploring strategies to alleviate proteolytic degradation through manipulation of glutamate feed concentrations and feeding strategies, and by coupling reaction and product separation into one processing unit.

The second bottleneck, involving the high selectivity of PCMH for *p*-cresol, causes the transient accumulation of *p*-hydroxybenzyl alcohol in batch culture. This constrains the available carbon flux that can be put through the pathway without accumulating intermediates. The transient accumulation of *p*-hydroxybenzyl alcohol in cultures of *P. putida* NCIB9869 growing on *p*-cresol is not observed due to the presence of an NAD$^+$-dependent alcohol dehydrogenase.[15] Co-expression of a *p*-hydroxybenzyl alcohol dehydrogenase with PCMH and PHBZ could be used to improve the carbon flux and minimize generation of the *p*-hydroxybenzyl alcohol intermediate seen during the conversion of *p*-cresol to HBA by resting cells of *P. putida* EM2878. The benzyl alcohol dehydrogenase, *xylB* product, from *P. putida* mt2 has been shown to possess sufficient substrate range and activity to be useful in such a manner.[19]

Initial catalyst development focused on *P. mendocina* KR1 for production of HBA from toluene. However, we were unable to obtain significant accumulation of HBA from toluene using this strain due to our inability to obtain a sufficient disruption of PobA activity. Nonetheless, we have demonstrated the technical feasibility of toluene conversion to HBA using a recombinant *P. putida*, and have captured much of the detail and laid much of the pertinent ground work toward the evolution of such a process.

Experimental

Chemicals

All chemicals used in kinetic studies and fed-batch fermentations were purchased from Sigma/Aldrich Chemical Co., St. Louis, MO, and were of the highest purity available. Restriction enzymes, calf intestinal phosphatase, and T4 DNA ligase were purchased from Promega Corp., Madison, WI.

Bacterial strains and plasmids

Bacterial strains and plamids used in this work are described in Table 3. *Escherichia coli* DH5α was used for routine plasmid maintenance and isolation of pUC18Not derivatives. *E. coli* S17-1λpir was used for maintenance of all mini-Tn*5* transposon systems, and as donor strain in mating experiments for mobilization of mini-Tn*5* systems into target *Pseudomonas* strains.

Media and cultivation

Luria broth (LB) was used for growth and maintenance of *P. putida* and all *E. coli* plasmid-bearing strains. *E. coli* and *P. putida* strains were incubated at 37 °C and 30 °C, respectively. Cell growth was monitored at 600 nm using a Shimadzu UV160U UV/visible recording spectrophotometer. For solid medium, 15 g l^{-1} agar was added to LB medium. Plate cultures were stored at 4 °C for up to 4 weeks and were used as sources of inoculum for overnight cultures in bioconversion experiments. Liquid cultures were stored long term in LB with 15% (v/v) glycerol at −70 °C. Bioconversion experiments using *P. putida* EM2878 were carried out in L-Salts minimal media[26] (minimal media) with 0.6% L-glutamate as carbon source. When appropriate, antibiotics were added at the following concentrations: ampicillin 200 μg ml^{-1}, kanamycin 50 μg ml^{-1}, and tetracycline 10 μg ml^{-1} for all *E. coli* strains; kanamycin 50 μg ml^{-1}, and tetracycline 50 μg ml^{-1} for *Pseudomonas* strains. Carbon sources and antibiotics were filter-sterilized and added to autoclaved minimal media separately except for toluene and *p*-cresol, which were added to the media directly.

N-Methyl-*N′*-nitro-*N*-nitrosoguanidine mutagenesis

N-Methyl-*N′*-nitro-*N*-nitrosoguanidine was used to disrupt *p*-hydroxybenzoate hydroxylase, PobA, activity in *P. putida* KT2440 as previously described.[27] Three rounds of enrichment using 100 μg ml^{-1} (+)-cycloserine and 200 μg ml^{-1} piperacillin were performed before plating onto 0.6% succinate minimal media plates. Mutant selection was accomplished by replica plating onto 5 mM HBA and 5 mM benzoate minimal media plates. Colonies showing no growth on HBA and positive growth on benzoate were further tested for loss of PobA activity in cell extracts by activity assay as described below.

PobA enzyme assay

Duplicate cultures for PobA activity assays were prepared as follows. Three ml of an overnight culture grown on 0.6% L-glutamate minimal media were transferred to 200 ml of 0.6% L-glutamate minimal media supplemented with 10 mM HBA or 1.5 mM *p*-hydroxybenzaldehyde, and allowed to grow to mid-exponential phase followed by centrifugation at 4 °C. Cell pellets were resuspended in 50 ml of minimal media supplemented with 0.06% L-glutamate and 10 mM HBA or 1.5 mM *p*-hydroxybenzaldehyde and allowed to grow for another 3 hours. Cells were then centrifuged at 4 °C and flash frozen in −70 °C 95% ethanol and stored at −70 °C for no more than 24 hours prior to assaying.

Cell extracts were prepared by washing frozen cell pellets in 10 ml of ice-cold 33 mM Tris-sulfate, 0.33 mM EDTA (pH 8.0) buffer and sonicating on ice in 5 ml of the same buffer for 3 minutes in 30 second bursts using a Fisher Sonic Dismembrator Model 300. Extracts were then centrifuged at 4 °C for 25 minutes at 14000 *g* in a Sorvall SS34 rotor (DuPont, Newtown, CT). Following centrifugation, extracts were immediately assayed in triplicate for NADPH turnover at 340 nm.[11]

Plasmid construction

Plasmid DNA was isolated by a modified alkaline lysis protocol of Birnboim and Doly.[28] Protocols for restriction digests, and ligations were carried out as described by the enzyme supplier. Methods for DNA isolation and purification, and electrophoresis have been described elsewhere.[29]

Construction of the mobile expression systems was based on the mini-Tn*5* transposon systems developed by deLorenzo *et al.*,[23] pKMY402 served as the source of *tmoABCDE*.[21] *pchCF*, the 2 genes encoding the cytochrome c and flavoprotein subunits,

Table 3 Bacterial strains and plasmids

Bacterial strain	Genotype/phenotype^a	Source or reference
E. coli DH5α	*supE*44 Δ*lacU*169(Φ80*lacZ*ΔM15), *hsdR*17, *recA*1, *endA*1, *gyrA*96, *thi*-1, *relA*1	Stratagene (La Jolla, CA)
E. coli S17-1λpir	*recA, thi, pro, hsdR, M*$^+$, RP4:2-Tc^R:Mu:Km^R, Tn*7*Tp^{R}Sm^R,λ*pir* lysogen	13
P. putida KT2440	*hsdR*	20
P. putida EM2839	*hsdR*, Pob$^-$	This work
P putida EM2840	*hsdR*, Pob$^-$, mini-Tn*5 aphA lacI*^{q} *Ptrc pchCF phbz*	This work
P. putida EM2871	*hsdR*, Pob$^-$, mini-Tn*5 tet nahR Psal tmoABCDE*	This work
P. putida EM2878	*hsdR*, Pob$^-$, mini-Tn*5 aphA lacI*^{q} *Ptrc pchCF phbz,* mini-Tn*5 tet nahR Psal tmoABCDE*	This work
Plasmid	Relevant marker^b	Source or reference
pKMY402	*bla, tmoABCDE*$^+$ RSF1010-*lacI*^{q}/*Ptac* broad-host-range expression vector; source of *tmoABCDE* genes	21
pUC18Not	*bla, α-lac, NotI*-M13mp18 MCS-*Not*I	22
mini-Tn5Tc	*bla,* mini-Tn*5 tet* in a pUT delivery plasmid; source of *tet* gene	23
pCNB4	*bla,* mini-Tn*5 aphA nahR Psal* in a pUT delivery plasmid	13
pCNB5	*bla,* mini-Tn*5 aphA lacI*^{q} *Ptrc* in a pUT delivery plasmid	13
p16SmaI	*bla, pchCF*$^+$ derivative of pUC18	24
pCNB4-Tc	*bla,* mini-Tn*5 tet nahR Psal* in a pUT delivery plasmid	This work
pESM6	*bla, phbz*$^+$ derivative of pUC18	25
pESM10	*bla, pchCF*$^+$, *phbz*$^+$ derivative of pUC18Not	This work
pESM14	*bla, pchCF*$^+$, *phbz*$^+$ derivative of pUC18Not	This work
pESM20	*bla, tmoABCDE*$^+$ derivative of pUC18Not	This work
pESM21	*bla, tmoABCDE*$^+$ derivative of pCNB4-Tc	This work
pESM23	*bla, pchCF*$^+$, *phbz*$^+$ derivative of pCNB5	This work

^{a} Tp^R, trimethoprim resistance; Sm^R, streptomycin resistance; Pob$^-$, no growth on HBA. ^{b} MCS, multiple cloning site.

respectively, of PCMH from *P. putida* NCIB9869, were obtained as a 2.9 kb *Sma*I fragment from p16*Sma*I.[24] *phbz* was cloned by PCR from a preparation of *P. putida* NCIB9866 genomic DNA and placed into the *Xba*I/*Hind*III sites in pUC18 giving pESM6.[25] Insertion of cloned genes into the unique *Not*I site downstream of *Ptrc* and *Psal* promoters in pCNB5 and pCNB4-Tc was accomplished using pUC18Not.[22] Partial restriction maps of the plasmids used during construction of the mobile expression systems are provided in Fig. 2.

The pathway for toluene conversion was set up in two regulatory units in order to minimize the inefficient transcription of distal genes. This was accomplished by placing the *P. mendocina* KR1 *tmoABCDE* genes encoding T4MO under *Psal* control, while *pchCF* and *phbz* were set under *Ptrc* promoter control. The genes encoding T4MO will be referred to as the upper pathway, while the genes encoding PCMH and PHBZ are referred to as the lower pathway. Construction of the upper pathway involved intermediate plasmids and modification of the initial pCNB4 mini-Tn*5* system. First, the 2.3 kb *aphA* gene, the kanamycin resistance locus of pCNB4, was replaced with the 2.2 kb *tet* gene of mini-Tn*5*Tc (tetracycline resistance) to facilitate selection of multiple Tn*5* insertions. *Xma*I digestion of pCNB4 yielded a 6.3 kb fragment that was ligated to similarly digested *tet* from mini-Tn*5*Tc to give pCNB4-Tc. The 5 structural genes encoding active T4MO were excised from pKMY402 by *Eco*RI and *Ssp*I digestion to give a 3.6 kb fragment that was ligated into *Eco*RI/*Sma*I digested pUC18Not, giving pESM20. *Ssp*I digestion was immediately downstream of the transcription terminator following *tmoE* in pKMY402.[21] *Not*I digestion of pESM20 and ligation of the *Not*I-*tmoABCDE*-*Not*I gene cluster into *Not*I digested pCNB4-Tc gave pESM21, Fig. 2(a).

Construction of pESM23, harboring the lower pathway, involved the construction of intermediate plasmids pESM10 and pESM14. First, the 2.9 kb *pchCF* fragment was excised from p16*Sma*I by *XmaI* digestion and ligated into *Xma*I digested pUC18Not yielding pESM10. In p16*Sma*I the 3′ end of *pchC* is 700 base pairs upstream of the 5′ end of *pchF*.[24] Following ligation of *pchCF*, the 1.5 kb *phbz* gene was cut from pESM6[25] with *Xba*I and *Hind*III and ligated into *Xba*I/*Hind*III digested pESM10 giving pESM14. This construction placed the 5′ end of *phbz* immediately next to the 3′ end of *pchF* in pESM14. *Not*I digestion of pESM14 yielded a 3.4 kb fragment containing *pchCF* and *phbz*, which was then ligated into *Not*I digested pCNB5, giving pESM23 (Fig. 2(b)).

Transposon mutagenesis

Mobilization of mini-Tn*5* constructs into *P. putida* EM2839 derivatives was carried out essentially as described by Harwood *et al.*[12] 10^{-2} to 10^{-4} dilutions of overnight matings on LB were plated onto 0.6% succinate minimal media plates with the appropriate antibiotic for selection of putative transconjugants. When tetracycline was used, the magnesium sulfate concentration in the minimal media was diluted 50-fold. Putative transconjugants were then screened for activity using the batch biotransformation procedure described below. Authentic transposition, as determined by loss of the pUT delivery system and return of colonies to piperacillin sensitivity, was assayed by picking colonies onto LB plates amended with 100 μg ml^{-1} piperacillin.

Batch transformation experiments

Duplicate overnight cultures were grown in 25 ml of 0.6% glutamate minimal media with the appropriate antibiotic. Five ml of overnight culture was then used to inoculate 200 ml of 0.6% glutamate minimal media without selection pressure in 500 ml flasks. When A_{600} was between 0.050 and 0.150, 2 mM IPTG and 0–10 mM salicylic acid were added to induce enzyme activity.

Induction was allowed to continue until cells reached late exponential phase, about 3.5 to 4 hours. At the end of the induction period, cells were harvested by centrifugation at 4 °C, and washed once with minimal media. The cell pellets were then resuspended at 2 × cell concentration in 100 ml of the same media used for growth and induction with 0–1.5 mM of toluene in 250 ml screw top flasks sealed with Teflon backed septa. For kinetic measurements, chloramphenicol was also added to 500 µg ml^{-1} to inhibit further protein synthesis. Samples (1 ml) were withdrawn periodically using a 3 ml syringe fitted with a 25 gauge 5/8 in needle and clarified by centrifugation. After decanting the supernatant, the cell pellets were then frozen at −70 °C until assayed for total protein. Supernatant fractions containing bioconversion products and intermediates were analyzed immediately by high performance liquid chromatography (HPLC) or frozen at −30 °C until analyzed. Activity values reported in text are the average ± the standard deviation of at least two independent determinations.

Fed-batch transformation experiments

Fed-batch toluene conversion to HBA was carried out in a 2 l jacketed Applikon fermentor (Applikon Dependable Instruments bv, The Netherlands). Toluene was fed in the gas phase by air stripping a toluene liquid feed delivered by a Perkin Elmer Series 10 Liquid Chromatograph HPLC pump (Perkin-Elmer Corp., Norwalk, CT). The liquid toluene flow-rate was fixed at 0.06 ml min^{-1} and a rotameter (Matheson, Montgomeryville, PA) was used to maintain the air flow-rate at 1.5 l min^{-1}. During the course of the fed-batch experiment, the reactor volume varied between 0.925 and 1.65 l. Temperature and agitation were kept constant at 30 °C and 850 rpm and pH was maintained at 7.1 ± 0.2 through the use of 3 M HCl. A 0.02% solution of antifoam in minimal media was used to control foaming and was fed at a rate equal to 10–12% of the total liquid flow-rate. Minimal media containing 1% glutamate as the growth carbon source, supplemented with 1 mM IPTG and 3 mM salicylate to induce enzyme activity, was used in a constant feeding policy for these studies.

Initially, 50 ml of an exponentially growing culture of *P. putida* EM2878 on 1% glutamate minimal media with 50 µg ml^{-1} of kanamycin and 50 µg ml^{-1} of tetracycline were used to inoculate the reactor containing 925 ml of minimal media without further selection pressure. After 6–7 hours of batch growth, the reactor was operated as a chemostat at a dilution rate of 0.1–0.15 h^{-1} for 4–5 residence times to allow for steady state induction of pathway genes. Once steady state was reached, the feed flow-rate was reduced to 23 ml h^{-1}, the exit liquid flow was stopped, and the toluene flow started into the reactor. Three ml samples were taken periodically to measure the glutamate, HBA, toluene, and protein concentrations in the reactor. In addition, 1 ml samples were diluted in minimal media without carbon source and plated on LB, LB supplemented with 50 µg ml^{-1} kanamycin or 50 µg ml^{-1} tetracycline, and 10 mM HBA minimal media plates to assess the stability of the transposon integration and frequency of reversion of Pob^{-} mutants. Prior to plating on HBA minimal media, cells were washed twice in miminal media.

Total protein determination

Cell pellets (1 ml) obtained in the batch bioconversion experiments were analyzed for total protein using a bicinchoninic acid kit (Pierce, Rockford, IL) with bovine serum albumin as standard. Cell pellets were resuspended in 1 ml 0.85% NaCl and sonicated as described for PobA enzyme assays.

Analytical

Identification and quantification of bioconversion products

Bioconversion products and intermediates were separated by HPLC using a reversed-phase Altima C18 column (Alltech Ltd., Deerfield, IL). Products were identified using a Waters 990 Photodiode Array Detector (Waters Chromatogrpahy Division, Milford, MA) by retention time and spectral comparison with known standards. Products were quantified using a previously determined correlation. Methanol and water acidified with 0.1% trifluoroacetic acid served as the mobile phase. Separation of HBA, *p*-hydroxybenzyl alcohol, *p*-cresol, *p*-hydroxybenzaldehyde, salicylic acid and chloramphenicol was accomplished using an initial 8 minute isocratic elution profile of 65% water and 35% methanol, then changing linearly over to 100% methanol in 10 minutes. The presence of salicylic acid and chloramphenicol in the media served as internal standards.

Quantification of liquid phase toluene concentrations

Liquid phase toluene concentrations were determined by GC analysis of pentane extracted aqueous samples. Aqueous samples (1 ml) were placed into 2 ml screw top glass vials, to which 250 µl of pentane containing 200 ppmv heptane (an internal standard) was added. Vials were then sealed with Teflon backed septa, shaken vigorously for 2 minutes, and allowed to phase separate. One µl of the pentane phase was then injected into a Hewlett Packard 5890 gas chromatograph (Hewlett Packard, Avondale, PA) equipped with a 10 m DB-624 capillary column (J&W Scientific, Folsom, CA) and flame ionization detector. Injector and detector temperatures were maintained at 220 °C and a column temperature of 65 °C. Helium was used as the carrier gas and was run splitless for the first 0.2 minutes, then split for 3.8 minutes at a split ratio of 1.13. Toluene concentrations were determined by comparison of area counts with a previously determined correlation.

SDS PAGE analysis of T4MO polypeptides

A 12% SDS PAGE gel was used to analyze the relative concentrations of selected T4MO polypeptides during fed-batch operation essentially as described by Laemmli.[30] Following electrophoresis and staining with Coomassie Brilliant Blue, selected T4MO bands were scanned using a Hoefer GS300 Transmittance/Reflectance Scanning Densitometer (Hoefer Scientific Instruments, San Francisco, CA) connected to a Fisher Series 5000 RecordAll Chart recorder.

Samples for SDS PAGE analysis were prepared as follows. Samples (30 ml) of fed-batch culture were collected and centrifuged for 10 minutes at 4 °C. Immediately following centrifugation, cell pellets were flash frozen in −70 °C 95% ethanol and stored at −70 °C. Pellets were thawed in 5 ml of deionized water containing 1 mM phenylmethyl sulfonyl fluoride as a protease inhibitor. Cells were sonicated for a total of 7.5 minutes and centrifuged for 25 minutes at 4 °C as previously described. Supernatant fractions from the above were then assayed for total protein. 50 µg of total soluble protein was loaded per lane.

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Enzymatic synthesis and NMR studies

of acylated sucrose acetates

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Summary

The lipase-catalyzed esterification of partially acetylated sucrose has been studied. It was shown that the chemical acetylation increased the reaction rate of the subsequent enzymatic acylation. Thus it was possible to perform the enzymatic acylation in the absence of solvents while underivatized sucrose did not react. From HMBC NMR spectroscopy, it was concluded that the main site of acylation was the 6-position of the fructose moiety.

Introduction

Sucrose fatty acid esters are of interest as nonionic emulsifying agents. They are derived from cheap and readily available raw materials and they are biocompatible and biodegradable. In their chemical synthesis, high temperatures are applied to overcome the incompatibility of reacting a polar and an apolar reactant.[1] This leads to colored byproducts and a mixture of sucrose esters. An additional problem is that regioselective acylation is exceptional[2] in most chemical methods.

Enzymatic catalysis might overcome these disadvantages since it is an elegant manner to regioselectively introduce ester groups in (poly)hydroxy compounds.[3] In the presence of lipase or protease, esterification proceeds under mild conditions without side reactions. The first enzymatic acylations of carbohydrates reported were performed in polar organic solvents such as pyridine and dimethylformamide because of solubility reasons.[4]

Methods have been developed which avoid the use of these solvents since the resulting sugar fatty acid esters are utilized in cosmetics or foodstuffs. For example, in the presence of a salt hydrate pair, sucrose was acylated in a solvent-free system.[5] Also, sucrose acetals were enzymatically acylated in apolar organic solvents.[6] Another method is to use solvents which dissolve the carbohydrate only partially. As the sugar ester dissolves in the medium, complete conversions can be attained if the rate of dissolution is fast enough. Indeed, enzymatic acylation of monosaccharides such as fructose and glucose proceeded in solvents such as *tert*-butyl alcohol,[7] *tert*-amyl alcohol,[8] acetone[9] or supercritical carbon dioxide.[10] Disaccharides are even less soluble although the rate of esterification depends on the sugar.[11] Sugars having a low melting point, such as isomaltulose and trehalose, are acylated at a substantially faster rate than sucrose and lactose which have a high melting point. Since a low melting point indicates a low crystal lattice energy, it was concluded that a sugar having a low crystal lattice energy is converted faster in enzymatic esterifications.

Our objective was therefore to increase the rate of enzymatic acylation of sucrose by disturbing its crystal lattice. This was done by partial chemical acetylation prior to the enzymatic reaction. It was shown that the acylation of the modified sucrose even proceeds in the absence of a solvent. The resulting acylated sucrose acetates were fully characterized by NMR analysis and the site of enzymatic acylation was determined.

Results and discussion

To facilitate the sequential enzymatic esterification, a chemical reaction was selected to disturb the crystal lattice of sucrose. The reaction had to satisfy certain conditions. An aqueous medium was preferred with regard to the solubility of sucrose. In addition, only a small modification of sucrose was permitted since the resulting fatty acid sucrose esters should maintain their emulsifying properties which make them attractive for application in cosmetics and personal care products. Partial acetylation of sucrose satisfied both conditions. It was assumed that sucrose fatty acid esters substituted with two acetyl groups have good detergent properties. For example, even fatty acid esters of an anomeric mixture of 1-*O*-ethyl-D-glucopyranosides are good detergents,[12] since the glucopyranoside polar head still contains three hydroxyl groups.

Increasing the conversion of enzymatic acylation of sucrose by prior chemical modification has been studied previously. This was achieved by conversion of sucrose into an acetal.[6] However,

Green Context

The development of biodegradable and biocompatible emulsifiers is a worthwhile goal. Sucrose carboxylates are a class of compounds which are particularly interesting candidates in this area. However, conventional acylation methods require harsh conditions and deliver poor quality products. This contribution describes a novel approach where sucrose is partially acylated chemically, and then acylation is completed enzymatically. NMR methods are used to define the nature of the products.

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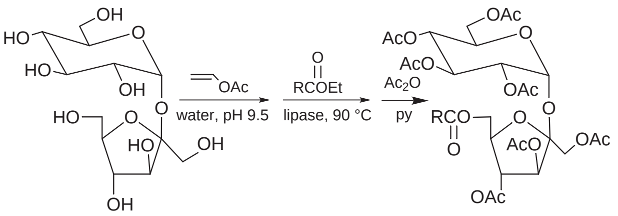
in contrast to partial acetylation, this reaction proceeded in *N*,*N*-dimethylformamide.

Hence, partial acetylation of sucrose with vinyl acetate in water was carried out (Scheme 1). Acetylation of carbohydrates with vinyl acetate is a routine reaction. For example, starch is acylated at the primary 6 and 6′ positions. However, this does not imply that these positions are protected from enzymatic acylation because interesterification reactions are also catalyzed by lipase.



Scheme 1 Lipase-catalyzed esterification of sucrose acetate and formation of the main product.

The acetylation of sucrose proceeded in 3 h at room temperature with 3 equivalents of vinyl acetate while the pH was kept at 9.4 by addition of 1 M NaOH. Products were simply isolated by evaporation of water and remaining vinyl acetate. A mixture of sucrose acetates was formed with an average degree of acetylation of 2 according to ^1H NMR analysis.

For the sequential enzymatic acylation of the sucrose acetates, the catalyst used was *Candida antarctica* lipase Novozym 435, a very robust enzyme which is known for its selectivity[14] and stability. For example, an anomeric mixture of 1-*O*-ethyl-D-glucopyranoside was esterified selectively at the primary 6-position in a melt of fatty acid at 70 °C.[12] We performed the reaction with long-chain fatty acid esters (ethyl palmitate and ethyl octanoate) in the absence of a cosolvent to make the reaction suitable for possible scale-up.

The reaction was shifted towards synthesis by removal of the ethanol formed under reduced pressure. The derivatization of sucrose indeed increased the reaction rate under these conditions. Sucrose acetate was converted to a degree of *ca.* 20% over 2 days. The conversion did not increase after longer reaction times. In contrast, no enzymatic esterification of unmodified sucrose was observed under the same conditions.

Thus, we have shown that a slight modification may increase the reactivity of sucrose in apolar solvents. Encouraged by this model study, other substituents are being studied for even higher activation of sucrose in apolar solvents.

The enzymatically esterified sucrose acetates were characterized by NMR analysis. To simplify the identification, the products were fully acetylated with acetic anhydride and isolated by chromatography over silica. For determination of the site of acylation, the connection through multiple ^1H–^{13}C bonds between ester carbonyls and sugar protons can be studied by 2D-heteronuclear proton-detected multiple-bond coherence (HMBC) NMR spectroscopy.[15] The HMBC spectrum for acylated/acetylated sucrose palmitate is shown in Fig. 1. The carbonyl ^{13}C signals between 168 and 170 ppm are assigned to the acetyl groups on basis of the cross-peaks with the acetyl CH_3 protons. Similarly, the carbonyl ^{13}C signals between 171 and 173 ppm are assigned to the acyl groups on basis of the cross-peaks with the acyl H-2 and H-3 protons. The attachment of an acyl group instead of an acetyl only results in a small difference in chemical shift for the sugar proton and carbon signals, since both groups are connected through ester bonds. Therefore, it was possible to obtain a complete assignment of the sugar signals, although acylation is heterogeneous. In the HMBC spectrum all possible cross-peaks resulting from three-bond couplings between sugar protons and acetyl-carbonyl are present. Cross-peaks with the acyl-carbonyl are at a low intensity, except for those with the fructose H-1 and glucose H-6, while the cross-peaks with fructose H-6 signals are prominent. A small but distinct cross-peak resulting from four-bond coupling between acyl H-2 and fructose C-6, but the absence of cross-peaks between acyl H-2 and other sugar carbons, confirms that the main acylation site is fructose at position 6. Since the intensities of cross-peaks in HMBC spectra depend on the value of the proton–carbon couplings and relaxation during the delay between the first proton and first carbon pulses in the pulse-sequence, they cannot be used for calculation of percentages of acylation.

From a 1D carbon spectrum, assigned on the basis of the HMBC spectrum, 75% acylation of fructose at C-6, 16% at glucose C-6, 4% at fructose C-1, and 1% or less at the remaining carbons was estimated. Similar results were found for sucrose octanoate (data not shown).

Conclusion

We have shown that the reaction rate of the enzymatic esterification of sucrose can be increased by chemical acetylation in advance of the enzymatic acylation. From HMBC NMR spectroscopy, it was concluded that the main site of acylation was the 6-position of the fructose moiety.

Experimental

General methods

Candida antarctica lipase Novozym 435, immobilized on an acrylic resin, was kindly donated by Novo Nordisk A/S, Denmark. Analytical TLC was carried out on precoated plastic TLC plates using methanol–CH_2Cl_2 (2:8, v/v) as the eluent. Spots were detected by charring with 10% (v/v) H_2SO_4 in methanol.

Synthesis of sucrose acetate

To a partial solution of sucrose (100 mmol, 34 g) in 70 ml water, vinyl acetate (300 mmol, 25.5 g) was added at once under stirring. NaOH (1 M) was added to raise the pH to 9.4. During the reaction, the mixture was stirred at room temperature while the pH was kept at 9.4 by addition of NaOH (1 M). After 3.5 h, the pH was lowered to 5.5 by addition of HCl (1 M) and the water was evaporated. The evaporated mixture was used without further purification for the next step. The mean degree of acetylation was 2.

Enzymatic esterification of sucrose acetate

Sucrose acetates (1 g), ethyl palmitate (2 g) and Novozym 435 (300 mg) were stirred under reduced pressure at 75 °C. After 20 h, the reaction mixture was solid. Additional ethyl palmitate (4 g) was added, the temperature was raised to 90 °C and the reaction mixture was stirred under reduced pressure for a further 24 h. The enzyme was removed by filtration and the reaction mixture was reacted with 20 ml pyridine and and 20 ml acetic anhydride (4 h, room temperature). After evaporation of the solvents under reduced pressure, the fully acetylated sucrose palmitates were separated by chromatography over silica [eluent: CH_2Cl_2–acetone (90:10 v/v)]. Peracetylated sucrose palmitates were isolated in a yield of 270 mg (13%). Similarly, sucrose acetates were acylated with ethyl octanoate at 90 °C during 2 days and peracetylated sucrose octanoates were isolated in a yield of 14%.

NMR analysis

Samples were dissolved in $CDCl_3$ (99.8 atom.% D). ^1H and ^{13}C NMR spectra were recorded at probe temperatures of 27 °C on a

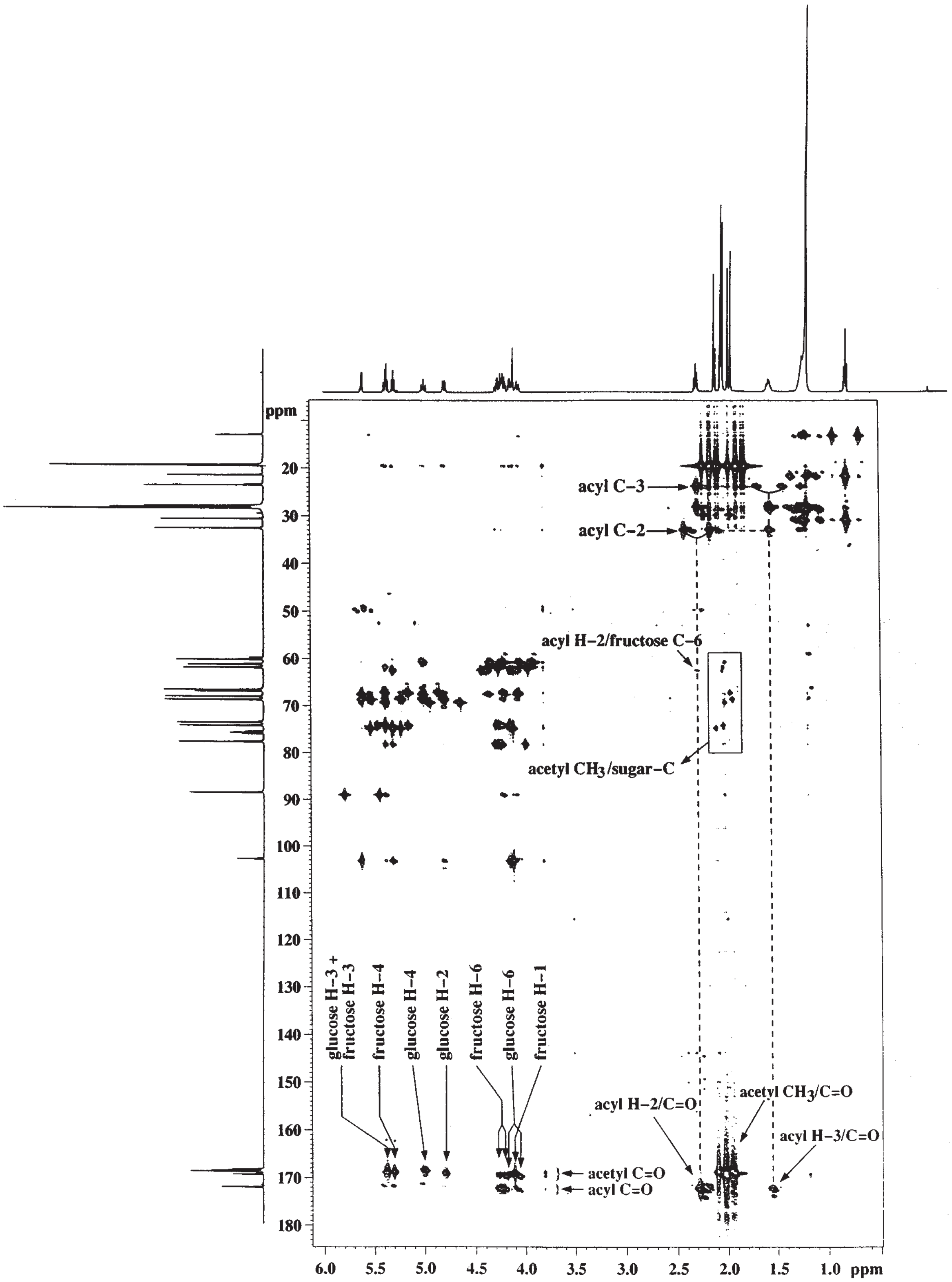


Fig. 1 500 MHz 2D ^{1}H–^{13}C HMBC spectrum of acylated/acetylated sucrose palmitate.

Bruker AMX 500 NMR spectrometer located at the Wageningen NMR Centre. The acetyl and acyl groups were localized by HMBC NMR spectroscopy.[16] A gradient-enhanced pulse sequence was constructed by changing the delay between the first proton and first carbon pulse in the standard gradient-enhanced 2D-heteronuclear proton-detected multiple-quantum coherence pulse-sequence delivered by Bruker to 50 ms. For sucrose palmitate 1024 experiments of 2048 data points, consisting of 40 scans per t_1 value, were recorded. Absolute-value Fourier transformation was performed resulting in a data set of 2048 × 1024 points. Chemical shifts are expressed in ppm relative to internal TMS (^{1}H, δ 0.0; ^{13}C, δ 0.0).

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K10 montmorillonite catalysis

C–C Bond formation by catalyzed conjugate addition and alkoxyalkylation of 1,3-dicarbonyl compounds

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Summary

The intrinsic catalytic properties of K10 and KSF montmorillonites allow the achievement of more environmentally acceptable procedures for C–C bond formation: Michael addition and α-alkoxyalkylation of 1,3-dicarbonyl compounds are performed by a convenient and cheap procedure based on the employment of montmorillonites as heterogeneous, reusable catalysts.

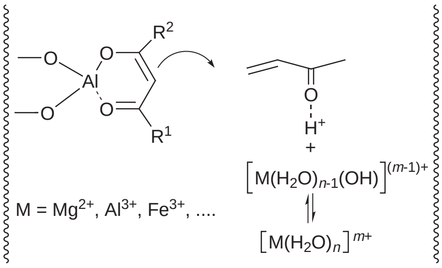
Introduction

Conjugate addition of 1,3-dicarbonyl compounds represents one of the most popular approaches for C–C bond formation, so that many procedures, involving basic or acidic conditions, have been proposed previously.[1] However, the occurrence in many cases of undesired competitive processes (bis-addition, intramolecular cyclization, rearrangement, *etc.*) has encouraged the use of alternative routes characterized by neutral conditions based, for example, on the employment of phase-transfer catalysts,[2] transition metal complexes,[3] lanthanides,[4,5] lithium iodide,[6] caesium fluoride,[7] dry alumina,[8] *etc.* Very interestingly, some years ago, Laszlo *et al.* reported an efficient route[9] implying dual catalysis with the Michael donor activated by nickel(II) bromide supported on a clay (K10-montmorillonite) and the Michael acceptor activated by iron(III) chloride.

Our recent investigations on the catalytic properties of commercial aluminosilicates (zeolites and clays)[10] suggested that a dual catalysis could be directly exerted by K10-montmorillonite, without incorporating any additional reactive species. Montmorillonites are crystalline aluminosilicates, whose multilayered structure is characterized by the presence of Lewis acidic sites (localized mainly on the edges of the layer) capable of activating Michael donors, and Brønsted acidic sites (localized mainly in the interlamellar region) capable of activating Michael acceptors (Scheme 1). Because of the occurrence of reactions in the interlamellar region, which can be considered a bidimensional reactor, satisfactory reaction rates can be reasonably expected, expecially after suitable modulation of the interlayer distance by water removal.

In order to verify the feasibility of the conjugate addition, in the preliminary phase, methyl vinyl ketone (MVK) and ethyl benzoyl acetate were chosen as representative reagents and their reactivity in the presence of commercially available K10-montmorillonite was investigated under a variety of experimental conditions.

As reported in Table 1, Michael addition was found to take place in all entries a–g, although different reaction times and yields were observed. First, it should be noted that a previous treatment of the catalyst involving microwave (MW) irradiation or conventional heating at 100 °C led to a noticeable reduction of reaction times (entries a, b and c). This result can be reasonably explained assuming that both MW and thermal treatment are responsible for water removal with a consequent increase of Brønsted acidity. Microwaves are known to preserve the structure and reactivity of the catalytic clay materials.[11,12]



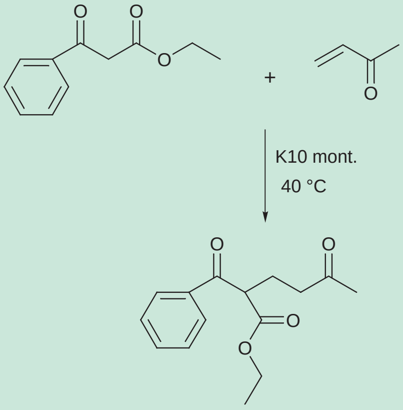
Scheme 1

Furthermore, the initial weight of the catalyst was found to decrease under both treatments (*ca.* 2%), and very similar results were usually obtained using either procedure (see entries e and f). From a preparative point of view, the reaction was shown to proceed both in weakly polar and in apolar solvents, indicating that the corresponding transition state could be stabilized by the polar microenvironment afforded by the catalyst.

Green Context

Two important processes for the construction of molecules (conjugate addition and alkoxyalkylation) can be carried out using commercially available and reusable clay catalysts. Reaction conditions are mild and relatively benign solvents such as hydrocarbons can be employed. Selectivity is also very good. Products of such reactions are industrially important, for example the use of alkoxyalkylation leads to intermediates in the production of quinolines, which are important as bioactive compounds. Addition reactions are similarly of widespread interest industrially, and have the real benefit of being 100% atom efficient with no co-products being formed. ***DJM***

Table 1 K10 montmorillonite catalysed Michael addition of ethyl benzoyl acetate on MVK



Entry	Solvent	Reaction time/h	Yield (%)^a
a	CCl_4	4	77^b
b	CCl_4	1	80
c	CCl_4	1	81^c
d	CH_2Cl_2	2	85
e	*n*-Hexane	18	68
f	*n*-Hexane	18	67^c
g	*n*-Hexane	18	65^d

[a] All yields refer to isolated chromatographically pure compounds. Unless otherwise indicated the catalyst was previously dried by MW irradiation (P = 300 W, 10 min). Ethyl benzoyl acetate:methyl vinyl ketone:catalyst ratio = 1 mmol:1.2 mmol:0.4 g. [b] H_2O not removed. [c] K10 montmorillonite was previously dried by heating at 100 °C overnight. [d] Value obtained using the recycled catalyst after a sequence of six identical experiments.

The higher reactivity and efficiency observed in halogenated solvents can be reasonably explained on the grounds of a more complete solubility of the reactive species in CH_2Cl_2 or CCl_4 than in *n*-hexane and, consequently, of an enhanced diffusion rate of the resulting solution in the interlayer region. Nevertheless, the results obtained in hydrocarbon solvents could be considered of synthetic value since they reveal access to an environmentally acceptable procedure based, primarily on the employment of a cheap, reusable catalyst, without any appreciable decrease of activity (entry g).

As confirmed by the data reported in Table 2, a very satisfactory degree of applicability was obtained with a variety of Michael acceptors (linear and cyclic unsaturated ketones) and donors (β-ketoesters, β-diketones, β-keto-α,γ-diesters).

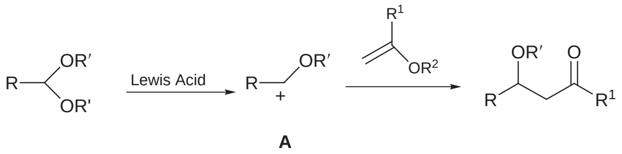
Steric factors, especially in the case of more hindered acceptors (entries h, j, k), proved to exert a strong influence on both efficiency and reaction rate, so that β,β-disubstituted alkenones (*e.g.* mesityl oxide and 3-methylcyclohex-2-en-1-one) were recovered completely unchanged after the usual treatment.

In every case, the employment of highly enolizable donors seemed to be an essential prerequisite: in fact, both diethyl malonate and Meldrum's acid failed to give conjugate addition.

However, we have found that a more acidic mineral clay, KSF montmorillonite, was capable of promoting Michael addition of very weak nucleophiles such as furans **4**.

No previous treatment of the catalyst was required and the reaction was shown to proceed with satisfactory yields and high selectivity (Table 3): although a competitive Diels–Alder reaction might be expected on the grounds of previous reports, no evidence of formation of the corresponding cycloadducts could be detected in the reported entries.[13,14]

A further fundamental process for C–C bond formation is represented by the α-alkoxyalkylation of carbonyl compounds (Scheme 2).[15] From a general point of view this reaction is an oriented cross-aldol condensation between two masked carbonyl compounds, an acetal (or ketal) and a silyl enol ether (or enol ester or enol ether). As regards the mechanistic aspects, the key step involves the formation of the electrophilic species **A** by reaction of the acetal with catalytic amounts of a Lewis acid and employment of the appropriate catalyst can allow high levels of diastereo- and enantio-selectivity to be reached.[16,17]



Scheme 2

Furthermore, it is noteworthy that satisfactory α-alkoxyalkylation of silyl enol ethers has been performed in the presence of Al-exchanged mineral clays.[18]

We deduced that the catalytic proprieties of *untreated* montmorillonites could be conveniently exploited for a very simplified procedure of α-alkoxyalkylation of 1,3-dicarbonyl compounds. In fact, it seemed reasonable that the generation of the electrophilic species **A** could have been promoted by Lewis acid sites situated on the surface of the catalyst or by Brønsted acid sites present in the interlayer region, while the intrinsic nucleophilicity of 1,3-dicarbonyl compounds should prevent their conversion into dienol silyl ethers.

A set of results obtained by submitting benzaldehyde dimethyl acetal, as a representative substrate, to the conditions reported in Table 4 has confirmed our assumption. Although the reaction was performed under heterogeneous conditions because of the absence of solvent and poor solubility of **1** in the acetal, α-alkoxyalkylation was usually found to take place with very appreciable efficiency. K10 montmorillonite seemed to present a more satisfactory combination of Lewis and Brønsted acidity than KSF montmorillonite which, probably because of its enhanced Brønsted acidity, caused rapid decomposition of the acetal. An analogous undesired process was observed by using either liquid acids (*e.g.* CF_3CO_2H, CF_3SO_3H) or solid acids (*p*-toluenesulfonic acid or Amberlyst H15). A control experiment, performed (Table 4, entry a) in the absence of any catalyst, afforded unchanged starting materials after prolonged reaction time (12 h).

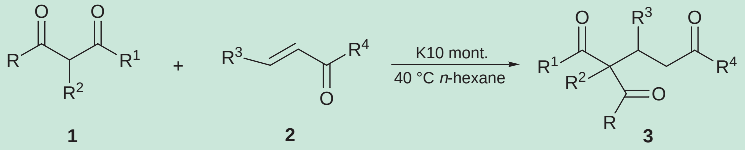
In reactions creating new stereogenic centers a poor degree of stereoselectivity was observed and, furthermore, the composition of the diastereoisomeric mixtures varied considerably after the purification procedure, probably as a consequence of the ready enolization of the 1,3-dicarbonyl moiety of **6**.

Attempts to extend this procedure to acetals of aliphatic aldehydes (*e.g.* phenylacetaldehyde dimethyl acetal and acetaldehyde dimethyl acetal) proved to be unsuccessful because of the very fast decomposition of the acetal to regenerate the carbonyl compound. These results suggested that a satisfactory applicability could be obtained only with substrates capable of forming strongly stabilized cations of type **A**.

In our opinon, 2,5-dihydro-2,5-dimethoxyfuran **8** (DHDMF), a cheap, commercially available compound, could represent a suitable acetal in a valuable test to confirm the above hypothesis.

In fact, we have found that upon treatment with **8** under the conditions reported in Table 5, starting materials **1** underwent a

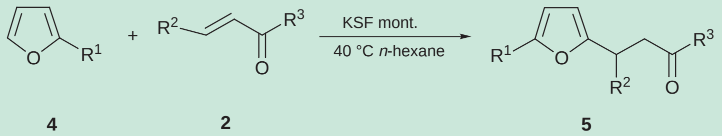
Table 2 K10 montmorillonite catalyzed conjugate addition of compounds **1**



Entry	R	R^1	R^2	R^3	R^4	Reaction time/h	Yield (%)[a]
a	Ph	OEt	H	H	Me	18	68
b	Ph	OEt	H	H	Me	2	85[b]
c	Me	OEt	H	H	Me	18	68
d	Me	OEt	H	H	Me	2	90[b]
e	Me	Me	H	H	Me	21	80
f	Ph	OEt	H	$–(CH_2)_3–$		24	65[c]
g	Ph	OEt	H	$–(CH_2)_3–$		24	33[b]
h	Me	Me	H	$–(CH_2)_3–$		46	65
i	Ph	Me	H	H	Me	20	74
j	Ph	Me	H	$–(CH_2)_3–$		43	45
k	Ph	Me	H	$–(CH_2)_3–$		43	43[b]
l	Ph	OEt	H	Me	Me	22	79[c]
m	Me	OEt	Et	H	Me	72	77
n	OEt	CO_2Et	Me	H	Me	24	59

[a] All yields refer to isolated chromatographically pure compounds. The structures of all the adducts were confirmed by ^{1}H NMR data (400 MHz) and by comparison with authentic samples.[6] Michael donor:Michael acceptor:catalyst ratio = 1 equiv.:1.2 equiv.:0.4 g. [b] Solvent: dichloromethane. [c] Michael adducts were obtained as a 1:1 diastereoisomeric mixture (^{1}H NMR analysis, 400 MHz).

Table 3 KSF montmorillonite catalyzed conjugate addition of furans **4**



Entry	Product	R^1	R^2	R^3	Reaction time/h	Yield (%)[a]
a	**5a**	Me	H	Me	0.75	86[b]
b	**5b**	Me	$–(CH_2)_3–$		23	42
c	**5c**	Me	Me	Me	23	54
d	**5d**	n-C_5H_{11}	H	Me	17	51
e	**5e**	n-C_5H_{11}	$–(CH_2)_3–$		22	61

[a] All yields refer to isolated chromatographically pure compounds, whose structures were assigned on the basis of ^{1}H NMR data (400 MHz). New compounds **5d**, **e** gave satisfactory elemental analyses. Furan derivative:Michael acceptor:catalyst ratio = 1 equiv.:1.2 equiv.:0.3 g; solvent: *n*-hexane. [b] No solvent. In this entry an excess of 2-methylfuran (4 equiv.) was used.

fast and efficient process of α-alkoxyalkylation leading to furans **9**, reasonably according to the reaction path indicated.

It is noteworthy that the reaction took place with high selectivity: in all entries unreacted starting materials **1** were recovered in 20–25% yields and, despite the rather severe reaction conditions, side processes of furan ring opening or β-fission of the 1,3-dicarbonyl moiety of **8** were not observed.

In conclusion, the intrinsic catalytic properties of commercially available K10 and KSF montmorillonites have been conveniently exploited for a variety of C–C bond formation reactions. No metal incorporation is required and the activity of the catalyst does not show any appreciable decrease after six recycles. The completely heterogeneous conditions allow an easy work-up (simply filtration under reduced pressure) and the use of more safe solvents (*n*-hexane or light petroleum) as an alternative to halogenated solvents is of benefit.

Experimental

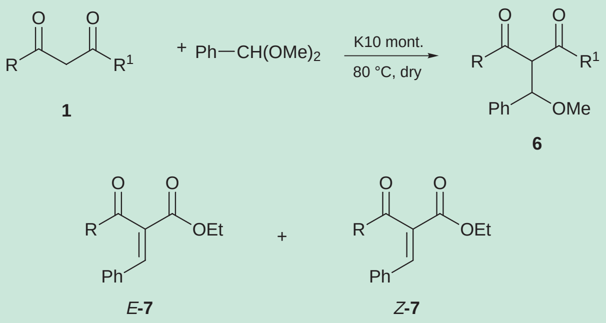
General

Unless otherwise noted, all reagents were obtained from commercial suppliers (Fluka or Aldrich) and were used without further purification. K10 montmorillonite and KSF montmorillonite were purchased from Fluka.

All reactions performed under MW irradiation were carried out in an Ace pressure tube (Aldrich) which was placed inside a MW kitchen oven (2450 MHz).

All reactions requiring anhydrous conditions were conducted under an argon atmosphere in flame dried glassware. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates and visualized using UV light followed by charring with 10% sulfuric acid–ethanol spray or 0.5% phosphomolybdic acid in 95% ethanol. Unless otherwise stated, standard work-up

Table 4 K10 montmorillonite catalyzed α-alkoxyalkylation of **1**



Entry	R	R^1	Reaction time/min	Yield (%)^a
a	Ph	OEt	45	86
b	Ph	Me	45	42
c	Ph	Ph	120	54
d	Ph	OEt	5	77^b
e	Me	OEt	60	80^c
f	Pr^i	OEt	30	83^{b,c}

[a] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by ^{1}H NMR data and by comparison with authentic samples. Acetal and **1** were used in 1:1 molar ratio. Catalyst and **1** were used in 1:1 weight ratio. No solvent. Final products of entries a, b and d were isolated as 1:1 diastereomeric mixtures (^{1}H NMR analysis, 400 MHz). [b] Conventional heating was substituted with microwave irradiation in a kitchen oven (P = 150 W). [c] The reported values refer to overall yields of elimination products **7** deriving from nearly quantitative loss of MeOH undergone by compounds **6** under the usual conditions. More exactly, chromatographic separation afforded pure *E*- and *Z*-isomers, respectively, in 55 and 25% yields (entry e), in 43 and 40% (entry f). New compounds *E*-**7** and *Z*-**7** gave satisfactory elemental analyses (see Experimental section).

refers to the combination of organic extracts, washing with brine and drying over anhydrous Na_2SO_4. Flash column chromatography was performed using Kieselgel 60 (Merk, 230–400 mesh).

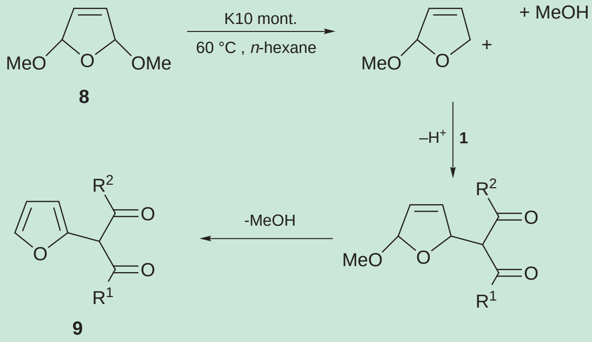
^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, with a Bruker DRX 400 MHz spectrometer. The chemicals shifts were measured on the δ scale relative to the residual signal of $CDCl_3$ (δ 7.26 and 77.0).

Typical procedure for Michael reactions

In a typical procedure, a mixture of 1,3-dicarbonyl compound (2 mmol), Michael acceptor (2.4 mmol) and K10 montmorillonite clay (0.8 g), previously microwave activated (power = 300 W, time = 10 min) in *n*-hexane or CH_2Cl_2 (3–4 ml) was stirred at 40 °C for different times. After the reaction was complete (TLC), the catalyst was filtered off and the product purified by chromatography (SiO_2, EtOAc–light petroleum) to afford adducts **3**.

2-Benzoyl-5-oxohexanoic acid ethyl ester **(3a)**
^{1}H NMR ($CDCl_3$): δ 8.0–7.5 (m, 5H), 4.4 (dd, 1H, J = 6.3, 6.4 Hz), 4.1 (q, 2H, J = 6.9 Hz), 2.6 (m, 2H), 2.3 (m, 2H), 2.1 (s, 3H), 1.1 (t, 3H, J = 6.9 Hz).

Table 5 K10 montmorillonite catalyzed α-alkoxyalkylation of DHDMF



Entry	R^1	R^2	Reaction time/min	Yield (%)^a
a	Ph	OEt	50	74
b	Ph	OEt	30	66^b
c	Ph	Me	60	73
d	Ph	Ph	90	52
e	Me	OEt	40	71
f	Pr^n	OEt	30	72
g	Pr^i	OEt	45	72
h	Ph	Me	30	66^b

[a] All yields refer to isolated chromatographically pure compounds, whose structures were confirmed by ^{1}H NMR data (400 MHz) and by comparison with authentic samples.[19] DHDMF:**1** molar ratio = 1:1. Catalyst:**1** weight ratio = 1:1. Solvent: *n*-hexane. [b] No solvent.

2-Acetyl-5-oxohexanoic acid ethyl ester **(3c)**
^{1}H NMR ($CDCl_3$): δ 4.2 (q, 2H, J = 6.9 Hz), 3.5 (t, 1H, J = 7.1 Hz), 2.5 (t, 2H, J = 7.1 Hz), 2.2 (s, 3H), 2.1 (s, 3H), 2.0 (m, 2H), 1.3 (t, 3H, J = 6.9 Hz).

3-Acetylheptane-2,6-dione **(3e)**
^{1}H NMR ($CDCl_3$); δ 3.6 (t, 1H, J = 6.8 Hz), 2.4 (t, 2H, J = 6.9 Hz), 2.2 (s, 6H), 2.1 (s, 3H), 2.0 (m, 2H).

3-Oxo-2-(3-oxocyclohexyl)-3-phenylpropionic acid ethyl ester **(3f)**
^{1}H NMR ($CDCl_3$): δ 8.0–7.5 (m, 5H), 4.3 (dd, 1H, J = 9.1 Hz), 4.2 (q, 2H, J = 6.9 Hz), 2.8 (m, 1H), 2.5–1.4 (m, 8H), 1.2 (t, 3H, J = 6.9 Hz).

3-(3-Oxocyclohexyl)pentane-2,4-dione **(3h)**
^{1}H NMR ($CDCl_3$): δ 3.6 (d, 1H, J = 10.1 Hz), 2.6 (m, 2H), 2.4–1.5 (m, 8H), 2.2 (s, 3H), 2.1 (s, 3H).

3-Benzoylheptane-2,6-dione **(3j)**
^{1}H NMR ($CDCl_3$): δ 8.0–7.5 (m, 5H), 4.6 (t, 1H, J = 6.9 Hz), 2.6 (dt, 2H, J = 6.2, 3.4 Hz), 2.2 (q, 2H, J = 6.9 Hz), 2.1 (s, 3H), 2.0 (s, 3H).

2-(3-Oxocyclohexyl)-1-phenylbutane-1,3-dione **(3k)**
^{1}H NMR ($CDCl_3$): δ 8.0–7.5 (m, 5H), 4.4 (d, 1H, J = 9.7 Hz), 2.9 (m, 1H), 2.4–1.6 (m, 8H), 2.2 (s, 3H).

2-Benzoyl-3-methyl-5-oxohexanoic acid ethyl ester **(3l)**
^{1}H NMR ($CDCl_3$): δ 8.0–7.5 (m, 5H), 4.4 (dd, 1H, J = 7.0, 7.7 Hz), 4.1 (q, 2H, J = 6.9 Hz), 2.9 (dd, 2H, J = 7.3 Hz), 2.6 (dq, 1H, J = 4.0 Hz), 2.0 (s, 3H), 1.1 (t, 3H, J = 6.9 Hz), 0.9 (dd, 3H, J = 6.8, 6.9 Hz).

2-Acetyl-2-Ethyl-5-oxohexanoic acid ethyl ester **(3m)**
^{1}H NMR (CDCl$_3$: δ 4.2 (q, 2H, J = 7.0 Hz), 2.3 (m, 2H), 2.1 (s, 6H), 2.0 (m, 2H), 1.8 (m, 2H), 1.3 (t, 3H, J = 7.0 Hz), 0.8 (t, 3H, J = 7.5 Hz).

2-Methyl-3-oxo-2-(3-oxobutyl)succinic acid diethyl ester **(3n)**
^{1}H NMR (CDCl$_3$): δ 4.3 (q, 2H, J = 7.4 Hz), 4.2 (q, 2H, J = 7.2 Hz), 2.4 (t, 2H, J = 7.7 Hz), 2.2 (t, 2H, J = 7.7 Hz), 2.1 (s, 3H), 1.4 (s, 3H), 1.3 (t, 3H, J = 6.9 Hz), 1.2 (t, 3H, J = 6.9 Hz).

4-(5-Methylfuran-2-yl)-butan-2-one **(5a)**
^{1}H NMR (CDCl$_3$): δ 5.9 (s, 1H), 5.8 (s, 1H), 2.8 (t, 2H, J = 6.2 Hz), 2.7 (t, 2H, J = 6.3 Hz), 2.2 (s, 3H), 2.1 (s, 3H).

3-(5-Methylfuran-2-yl)cyclohexanone **(5b)**
^{1}H NMR (CDCl$_3$): δ 5.9 (s, 1H), 5.8 (s, 1H), 3.1 (m, 1H), 2.6–1.8 (m, 8H), 2.2 (s, 3H).

4-(5-Methylfuran-2-yl)pentan-2-one **(5c)**
^{1}H NMR (CDCl$_3$): δ 5.8 (m, 2H), 3.3 (m, 1H), 2.8 (dd, 1H, J = 6.0, 16 Hz), 2.5 (dd, 1H, J = 8.0, 16 Hz), 2.2 (s, 3H), 2.1 (s, 3H), 1.2 (d, 3H, J = 7.0 Hz).

4-(5-Pentylfuran-2-yl)butan-2-one **(5d)**
^{1}H NMR (CDCl$_3$): δ 5.9 (s, 1H), 5.8 (s, 1H), 2.8–2.7 (dt, 2H), 2.5 (t, 2H, J = 7.6 Hz), 2.1 (s, 3H), 1.6 (m, 2H), 1.3 (m, 6H), 0.8 (t, 3H, J = 7.0 Hz). Found C, 75.42; H, 10.02; Calc. C, 75.00; H, 9.70.

3-(5-Pentylfuran-2-yl)cyclohexanone **(5e)**
^{1}H NMR (CDCl$_3$): δ 5.9 (s, 1H), 5.8 (s, 1H), 3.1 (m, 1H), 2.6–1.8 (m, 8H), 1.6 (m, 2H), 1.3 (m, 6H), 0.8 (t, 3H, J = 7.0 Hz). Found C, 77.38; H, 10.01; Calc. C, 76.90; H, 9.50.

Typical procedure for α-alkoxyalkylation reactions

In a typical procedure, a mixture of 1,3-dicarbonyl compound (2 mmol), acetal (2 mmol) and K10 montmorillonite clay (0.3–0.5 g) was stirred at 80 °C for different times. After the reaction was complete (TLC), the catalyst was filtered off and the product purified by chromatography (SiO$_2$, EtOAc–light petroleum) to afford adducts **6**.

2-(Methoxyphenylmethyl)-3-oxo-3-phenylpropionic acid ethyl ester **(6a)**
^{1}H NMR (CDCl$_3$): δ 8.0 (d, 2H, J = 7.60 Hz), 7.6–7.3 (m, 8H), 5.07 (d, 1H, J = 10.0 Hz), 5.06 (d, 1H, J = 10.0 Hz), 4.82 (d, 1H, J = 10.0 Hz), 4.79 (d, 1H, J = 10.0 Hz), 4.23 (m, 2H), 3.9 (q, 2H, J = 7.2 Hz), 3.2 (s, 3H), 3.1 (s, 3H), 1.2 (t, 3H, J = 7.2 Hz), 0.9 (t, 3H, J = 7.2 Hz).

2-(Methoxyphenylmethyl)-1-phenylbutane-1,3-dione **(6b)**
^{1}H NMR (CDCl$_3$): δ 8.0 (d, 2H, J = 7.60 Hz), 7.6–7.3 (m, 8H), 5.2–5.0 (m, 1H), 4.9 (d, 1H, J = 10.0 Hz), 3.2 (s, 3H), 3.1 (s, 3H), 2.3 (s, 3H), 1.89 (s, 3H).

2-(Methoxyphenylmethyl)-1,3-diphenylpropane-1,3-dione **(6c)**
^{1}H NMR (CDCl$_3$): δ 8.2–7.2 (m, 15H), 5.8 (d, 1H, J = 9.5 Hz), 5.3 (d, 1H, J = 9.5 Hz), 3.1 (s, 3H).

2-Acetyl-3-phenylacrylic acid ethyl ester **(*E*-7e)**
^{1}H NMR (CDCl$_3$): δ 7.66 (s, 1H), 7.37 (s, 5H), 4.29 (q, 1H, J = 7.0 Hz), 2.3 (s, 3H), 1.32 (t, 3H, J = 7.0 Hz).

2-Acetyl-3-phenylacrylic acid ethyl ester **(*Z*-7e)**
^{1}H NMR (CDCl$_3$): δ 7.57 (m, 1H), 7.40 (m, 5H), 4.32 (q, 1H, J = 7.0 Hz), 2.4 (s, 3H), 1.27 (t, 3H, J = 7.0 Hz).

2-Isobutyryl-3-phenylacrylic acid ethyl ester **(*E*-7f)**
^{1}H NMR (CDCl$_3$): δ 7.59 (s, 1H), 7.40 (m, 5H), 4.32 (q, 2H, J = 7.4 Hz), 3.1 (m, 1H), 1.2 (d, 2H, J = 6.9 Hz).

2-Isobutyryl-3-phenylacrylic acid ethyl ester **(*Z*-7f)**
^{1}H NMR (CDCl$_3$): δ 7.77 (s, 1H), 7.36 (m, 5H), 4.27 (q, 2H, J = 7.4 Hz), 2.6 (m, 1H, J = 6.9 Hz), 1.0 (d, 2H, J = 6.9 Hz).

2-Furan-2-yl-3-oxo-3-phenylpropionic acid ethyl ester **(9a)**
^{1}H NMR (CDCl$_3$): δ 7.9 (d, 2H, J = 7.2 Hz), 7.4 (m, 3H), 6.4 (d, 1H, J = 3.0 Hz), 6.3 (dd, 1H, J = 1.7, 3.0 Hz), 5.7 (s, 1H), 4.2 (q, 2H, J = 7.0 Hz), 1.2 (t, 3H, J = 7.0 Hz).

2-Furan-2-yl-1-phenylbutane-1,3-dione **(9c)**
^{1}H NMR (CDCl$_3$): δ 7.9 (d, 1H, J = 1.7 Hz), 7.3 (m, 5H), 6.3 (dd, 1H, J = 1.9, 3.0 Hz), 6.0 (d, 1H, J = 3.0 Hz), 2.1 (s, 3H).

2-Furan-2-yl-1,3-diphenylpropane-1,3-dione **(9d)**
^{1}H NMR (CDCl$_3$): δ 18 (s, 1H), 7.9 (s, 1H), 6.8 (s, 1H), 6.6 (s, 1H), 6.4 (s, 1H), 6.2 (dd, 1H, J = 3.2 Hz), 5.9 (d, 1H, J = 3.2 Hz).

2-Furan-2-yl-3-oxobutyric acid ethyl ester **(9e)**
^{1}H NMR (CDCl$_3$): δ 13 (s, 1H), 7.9 (d, 2H, J = 7.2 Hz), 7.4 (m, 3H), 6.4 (d, 1H, J = 3.0 Hz), 6.3 (dd, 1H, J = 1.7, 3.0 Hz), 5.7 (s, 1H), 4.2 (q, 2H, J = 7.0 Hz), 1.2 (t, 3H, J = 7.0 Hz).

2-Furan-2-yl-3-oxohexanoic acid ethyl ester **(9f)**
^{1}H NMR (CDCl$_3$): δ 13 (s, 1H), 7.4 (s, 1H), 6.4 (m, 1H), 6.2 (d, 1H, J = 3.0 Hz), 4.8 (s, 1H), 4.2 (q, 2H, J = 7.0 Hz), 2.2 (t, 2H, J = 7.4 Hz), 1.6 (m, 2H), 1.2 (t, 3H, J = 7.0 Hz), 0.9 (t, 3H, J = 7.0 Hz).

2-Furan-2-yl-4-methyl-3-oxopentanoic acid ethyl ester **(9g)**
^{1}H NMR (CDCl$_3$): δ 13 (s, 1H), 7.4 (m, 1H), 6.4 (m, 1H), 6.2 (d, 1H, J = 2.8 Hz), 4.9 (s, 1H), 4.2 (q, 2H, J = 7.0 Hz), 2.5 (t, 2H, J = 7.4 Hz), 1.2 (t, 3H, J = 7.0 Hz), 1.0 (t, 3H, J = 7.0 Hz).

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Paper 9/02102G

One-pot synthesis of coumarins

Catalysis by the solid base, calcined Mg–Al hydrotalcite

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Summary

The synthesis of coumarins (2*H*-benzopyran-2-ones) *via* Knoevenagel condensation over a recoverable, inexpensive solid base catalyst, calcined Mg–Al hydrotalcite, is reported for the first time. This method produces substituted coumarins in very high yields (>85%) and selectivities (*ca.* 100%) when aromatic hydroxy aldehydes are reacted with 2-substituted ethyl acetate.

Introduction

Many of the steps involved in the synthesis of fine chemicals and pharmaceuticals make use of large quantities of reagents such as mineral acids, bases and functionalizing agents. As a result, the *E*-factor (weight of by-product per unit weight of product) is large, being in the range 5–100.[1] The large yields of the by-products lower the atom efficiencies of the processes, waste valuable raw materials and necessitate expensive waste treatments lowering their overall economics. The development of alternative environmentally benign synthetic routes is thus of primary concern. In this connection, the use of environmentally friendly heterogeneous catalysts assumes significance as it results in waste minimization, safer operating conditions and easier product work-up. Though the use of solid acids such as clays and zeolites as 'green' catalysts has been well established,[2,3] the use of solid bases is much less developed.[4,5]

Hydrotalcites (HT) like anionic clays are a new family of interesting materials with applications as catalysts, catalyst supports, ion-exchangers and composite materials,[6] and are represented generally by the formula $Mg_6Al_2(OH)_{16}\cdot 4H_2O$. Upon thermal calcination at *ca.* 723 K these compounds lead to the formation of highly basic mixed metallic oxides with moderate surface area which are potential catalysts for various base-catalyzed condensation reactions.[7–9]

Coumarins (2*H*-benzopyran-2-ones) occupy a special role in the realm of natural and synthetic organic chemistry. Bishydroxy coumarins, warfarin and psoralen are known[10] for their anti-platelet and anti-tumor activities respectively. Of late, there has been some interest in the preparation and evaluation of biological properties of compounds possessing α-methylene-γ-butyrolactone groups either at C-4 or C-7 positions linked through a heteroatom (oxygen) in their demonstration as platelet aggregation inhibitors.[11] Several 3-substituted 7-hydroxycoumarins rank among the most efficient photostable laser dyes.[12]

The well known synthetic routes to coumarins including the Perkin, Raschig, Pechmann, Knoevenagel and Wittig reactions suffer from the requirement for the use of drastic conditions (acidic or basic), multiple steps, complicated synthetic operations and lengthy work-up procedures. Synthesis of 7-hydroxycoumarins catalyzed by solid acid catalysts has been reported by Hoefnagel *et al.*[13] A pharmacologically interesting chalcone vesidryl was synthesized[14] *via* a Clasien–Schmidt condensation catalyzed by HT-like compounds; similarly, Knoevenagel condensation was applied in the synthesis[15] of citronitril. Recently, Jacobs and coworkers[16] have reported the synthesis of 3-cyanocoumarin using 1,5,7-triazabicyclo[4.4.0]dec-5-ene immobilized in MCM-41 in moderate yield (58%). Here, we report an efficient, high-yielding, one-pot synthesis of coumarins *via* Knoevenagel condensation catalyzed by a cheap and easily prepared calcined Mg–Al hydrotalcite like anionic clay.

Experimental

Three Mg–Al hydrotalcites with Mg:Al atomic ratios of 2, 3 and 4 [Mg–Al 2.0 HT, Mg–Al 3.0 HT and Mg–Al 4.0 HT] were prepared by a co-precipitation method at constant pH (≈10) by reacting an aqueous solution of a mixture of $Mg(NO_3)_2$ and $Al(NO_3)_3$ with an aqueous solution of a mixture of NaOH (2–3 M) and Na_2CO_3 (0.2–0.35 M) at room temperature.[6] The resulting heavy slurry was aged at 338 K for 30 min with vigorous stirring. The precipitate was then filtered, washed several times with demineralized water and dried in air at 383 K overnight (to obtain the dried sample, HT). Calcination of the sample (to obtain the sample, CHT) was carried out in air at 723 K.

In a typical Knoevenagel condensation, the freshly calcined catalyst (10% w/w) was added to a mixture containing equivalent amounts of the appropriate phenol and a 2-substituted ethyl acetate in toluene (30 ml) under argon. The mixture was refluxed for 3–4 h at 353 K after which the product was isolated by standard procedures and characterized by IR and NMR spectroscopies.

Results and discussion

The results of the screening experiments carried out on the different hydrotalcite samples and other catalytic materials are presented in Table 1. No reaction was observed over the strongly acidic H-ZSM-5 or basic Cs-X. Pure MgO was slightly active, whereas Al_2O_3 was inactive. Mg–Al 3.0 CHT (calcined hydrotal-

Green Context

The use of base catalysis in organic synthesis is of great importance. Less has been done in the development of solid bases as green alternative solution phase base catalysts, which must often be separated by neutralisation. One of the more promising classes of solid bases is the hydrotalcites. These are clays, but, unusually, are basic rather than weakly acidic unlike the more common clays. The application of these materials discussed in this paper is the synthesis of coumarins, important biologically active materials, for which clean synthetic methods are required. The use of hydrotalcites leads to good yields of product, better than other, alternative bases. ***DJM***

Table 1 Condensation of salicylaldehyde with diethyl malonate and ethyl cyanoacetate in the presence of solid catalysts[a]

Entry	Catalyst	Diethyl malonate yield (%)	Ethyl cyanoacetate yield (%)
1	Mg–Al 2.0 CHT	40	48
2	Mg–Al 3.0 CHT	83	95
3	Mg–Al 3.0 HT[b]	15	60
4	Mg–Al 3.0 HT[c]	45	95
5	Mg–Al 4.0 CHT	35	60
6	MgO[d]	12	23
7	Al_2O_3[e]	No reaction	No reaction
8	CsX-Zeolite	No reaction	No reaction
9	H-ZSM-5	No reaction	No reaction

[a] Conditions: 18.77 mmol salicylaldehyde, 18.77 mmol diethyl malonate or ethyl cyanoacetate, 10% (w/w) of catalyst, toluene (30 ml) at 353 K for 4 h. [b] Uncalcined hydrotalcite. [c] Catalyst, 50% (w/w). [d] MgO obtained from decomposition of precipitated $Mg(OH)_2$. [e] Al_2O_3 obtained from decomposition of precipitated $(Al(OH)_3$.

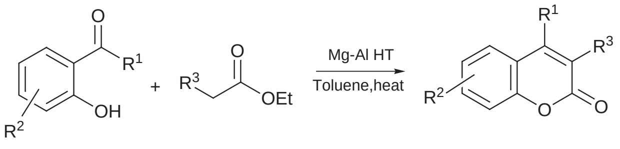
Table 2 Knoevenagel condensations catalysed by Mg–Al 3.0-CHT[a]

Entry	Phenol	2-Substituted ethyl acetate	Product	Yield (%)[b]
1	Salicylaldehyde	EAA[c]	3-Acetylcoumarin	83
2	Salicylaldehyde	DEM[c]	3-Ethylcoumarin carboxylate	87
3	Salicylaldehyde	ECA[c]	3-Cyanocoumarin	93
4	Salicylaldehyde	EA[c]	Coumarin	24[d]
5	*o*-Hydroxyacetophenone	ECA	3-Cyano-4-methylcoumarin	92
6	*o*-Hydroxyacetophenone	EAA	3-Acetyl-4-methylcoumarin	87
7	*o*-Vanillin	EAA	3-Acetyl-8-methoxycoumarin	87
8	*o*-Vanillin	ECA	3-Cyano-8-methoxycoumarin	85
9	*o*-Vanillin	DEM	8-Methoxy-3-ethylcoumarin carboxylate	92

[a] Conditions: 18.77 mmol salicylaldehyde, 18.77 mmol 2-substituted ethyl acetate, 10% (w/w) of catalyst, toluene (30 ml) at 353 K for *ca.* 4 h. [b] Yields are based on the aldehyde. [c] EAA = Ethyl acetoacetate, DEM = diethyl malonate, ECN = ethyl cyanoacetate, EA = ethyl acetate. [d] 48 h.

cite) was found to be the most active while Mg–Al 4.0 CHT and Mg–Al 2.0 CHT were less active. The uncalcined sample gave a low yield (*ca.* 15%) with diethyl malonate but a yield of nearly 60% with ethyl cyanoacetate.

Thus, Knoevenagel condensation of various phenols with 2-substituted ethyl acetates gave the coumarins in good yields (Scheme 1) in the presence of 10% (w/w) of Mg–Al 3.0 CHT in refluxing toluene for *ca.* 4 h. Toluene was chosen as the solvent after screening several other solvents such as ethanol, THF, dioxane, methanol, benzene, *etc.* The order of reactivity of the reagents (Table 2) was found to be cyanoethyl acetate > diethyl malonate > ethyl acetoacetate > ethyl acetate. Malonic acid did not undergo any reaction and this may be attributed to poisoning of the basic sites of the catalyst by malonic acid. 3-Cyanocoumarin was obtained in 93% isolated yield and 3-cyano-8-methoxycoumarin was obtained in 85% yield.



R^1 = H, Me
R^2 = H, OMe
R^3 = H, CN, COMe, CO_2Et

Scheme 1

Conclusions

The results demonstrate that Knoevenagel condensation with suitably activated Mg–Al hydrotalcite results in the efficient, mild and effective synthesis of several substituted coumarins with nearly 100% selectivity. This method thus offers a practical alternative to conventional bases and the process itself is environment friendly with minimal waste.

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Water promoted organic chemistry

The allylation of carbonyl (and acetal) compounds by tetraallylstannane

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Summary

A mild and effective water based procedure for the allylation of acetals, alkanals and alkanones is described. This procedure successfully minimises the environmental impact of tetraallylstannane by allowing isolation of the inorganic stannane salts and recycling of the organic solvents used to extract the homoallylic alcohol products. Yields are good to excellent.

Introduction

Allylation of carbonyl compounds, by a variety of allylic metals, is synthetically analogous to Aldol condensation,[1] but allows for the subsequent manipulation of the alkene moiety.[2] This addition can be achieved with high regio- and stereo-selectivity, but in the case of allyl- and alkyl-stannanes, is often plagued with difficulties in the removal of the organostannane by-products. Although allylation is usually promoted by the addition of Lewis acid,[3] high pressure[4] or heat,[5] there is a growing body of evidence that, in certain circumstances, the solvent (THF–HCl[6] or methanol[7]) can promote a facile allyl transfer from tetraallylstannane **1** to alkanals, alkanones and (in the presence of TFA or SiO_2) acetals.[8]

However, the use of organostannanes is fraught with serious environmental implications, such that a great deal of effort has been directed towards the development of more environmental friendly stannane reagents, *e.g.* water soluble[9] and polymer supported organostannanes.[10]

Recently there have been reports of indium mediated allylation reactions conducted in water and aqueous THF.[11] We were thus encouraged to further develop our existing methanol promoted allylation procedure.

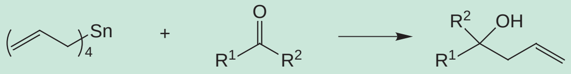
In the solvent promoted allylation procedure, no contamination of the homoallylic alcohol by organostannane residues occurs after a simple extractive work-up, thus improving the synthetic utility of stannanes from an environmental viewpoint. Additionally, the resultant inorganic stannane salts are easily isolated following freeze drying of the aqueous phase.

Herein, we report our efforts in developing this procedure under conditions which require minimal energy input (stirring at room temperature in the case of acetals) and minimise environmental impact through a simple work-up and by trapping of the inorganic stannanes.

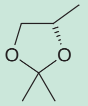
Results and discussion

We have examined the allylation of a series of alkanals (Table 1, entries 1–6), and alkanones (Table 1, entries 7–10) with tetraallylstannane **1** in aqueous solutions. Tetraallylstannane and the alkanal were stirred vigorously in the presence of water at room temperature (typically 25 °C) for 24 h. After extractive work-up (EtOAc) examination of the reaction mixture (by ^1H and ^{13}C

Table 1 Yields of homoallylic alkanols after addition of **1** to alkanals in the presence of water



1 **2** **3**

Entry	Compound	R^1	R^2	Product	Yield (%)
1	**2a**	Ph	H	**3a**	94[a]
2	**2b**	$PhCH_2$	H	**3b**	96[a]
3	**2c**	*p*-MeC_6H_4	H	**3c**	90[a]
4	**2d**	*p*-ClC_6H_4	H	**3d**	84[a]
5	**2e**	Me_2CH	H	**3e**	73[b]
6	**2f**		H	**3f**	98[c]
7	**2g**	Me	Me	**3g**	74[d]
8	**2h**	$–(CH_2)_5–$		**3h**	77[d]
9	**2i**	$–CH{=}CH(CH_2)_3–$		**3i**	28[d]
10	**2j**	Ph	Me	**3j**	55[d]

[a] Isolated yield. [b] Isolated by fractional distillation. [c] Cram product *erythro*, de ≈70%. [d] Reflux 24 h.

Green Context

The use of water in organic reactions is generally considered beneficial, as it is environmentally more benign than organic solvents, and avoids the generation of volatile organics, which have to be strictly controlled. In this work, there is an additional benefit in that the use of water improves the isolation of the environmentally unfriendly tin containing byproducts. Thus, the atom efficient reaction is accompanied by an excellent separation of the byproducts in a benign solvent. ***DJM***

NMR spectroscopy) indicated smooth conversion to the anticipated homoallylic alkanols. No trace of organostannane residues was apparent.

As can be seen from Table 1, excellent yields of **3a–f** are obtained after stirring at room temperature whilst only moderate yields of **3g–j** are obtained even after reflux. Even during competition experiments using equimolar amounts of alkanals and alkanones, only the alkanal was allylated at room temperature. Thus there is a significant degree of selectivity in the reaction, even with more reactive alkanones (*e.g.* **2g**). Interestingly, in this instance we observed a significant yield improvement with reflux at 100 °C in water for alkanones **3i** and **3j** than we have previously observed in the corresponding methanol promoted reaction (<1% to 28% and *ca.* 20% to 55% respectively).[7b] This presumably is more an artefact of the change in reflux temperature than a change in mechanism. We have previously proposed that hydrogen bonding between the carbonyl compound and methanol is the predominant activating effect, and an eight-membered transition state involving water coordination to tin and hydrogen bonding to the carbonyl compound can be invoked. An extension of this proposal accounts for the corresponding HCl-mediated reaction and the water promoted reactions presented herein (Fig. 1).[7b]

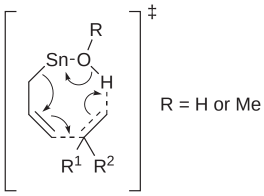


Fig. 1 Proposed transition state for the methanol- and water-mediated addition of allylic stannanes to carbonyl compounds.

In previous studies we have demonstrated the one-pot allylation of acetals in the presence of **1** and equimolar amounts of TFA or SiO_2 (with TFA being more efficient). We have now examined the reactions of two acetals with TFA, **1** and water. The yields are very good and are listed in Table 2.

Experimental

General procedure for allylations of alkanals and alkanones with 1

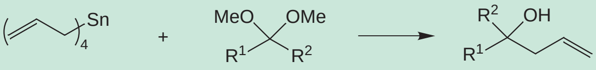
Carbonyl compounds (**2**, 10 mmol) and tetraallylstannane (2.5 mmol) were stirred vigorously together in a round bottomed flask containing water (10 mL). For alkanals the reaction was stirred at *ca.* 25 °C for 24 h; alkanones were refluxed for 24 h. The mixtures were then extracted with ethyl acetate (3 × 25 mL), dried (Na_2SO_4), and the solvent removed *in vacuo* or by fractional distillation for particularly volatile products (*e.g.* **3c**). The organic solvent could then be used (after distillation) for repeated extractions. Alkanal products were typically >90% pure by ^{1}H NMR, however alkanone products required chromatography (speedy column, silica gel, ethyl acetate) to obtain pure materials. The identity of the products was confirmed by comparison with literature ^{1}H and ^{13}C NMR data (see ref. 3 and references cited therein.)

Freeze drying of the aqueous phase allowed isolation of solid inorganic stannane residues.

General procedure for allylations of acetals

As above with the addition of equimolar quantities of TFA (10 mmol).

Table 2 Yields of homoallylic alkanols on treatment with TFA and **1**



1 **4** **3**

Entry	Compound	R^1	R^2	Product	Yield (%)
1	**4a**	Ph	H	**3a**	98
2	**4b**	$PhCH_2$	H	**3b**	85

[a] Isolated yield, prepared as illustrated in ref. 10.

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Synthetic studies on stoichiometric reaction gels of $AlPO_4$-5

for the purpose of minimising solvent waste

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Summary

The stoichiometric synthesis of the molecular sieve $AlPO_4$-5 was achieved using a gel of composition $(CH_3CH_2)_3N:Al_2O_3:P_2O_5:10H_2O$ at 200 °C. ICP measurements on the mother liquor showed that a conversion of 97% had been achieved.

Introduction

A series of aluminophosphate molecular sieves, $AlPO_4$-*n*, was first reported by Wilson *et al.* in 1982.[1] $AlPO_4$-5 is a member of this series with large pores, an uncharged framework and excellent thermal stability. As the best investigated molecular sieve in its family, $AlPO_4$-5 has potential commercial applications in industry,[2–3] where it can be used either as an absorbent or as an excellent shape-selective supporting carrier for catalysts.

The synthesis of $AlPO_4$-5 usually employs a gel of the following composition: $R:Al_2O_3:P_2O_5:40H_2O$, where R is an organic templating agent.[4] However, the yield in this synthetic route is low. Our experiments have confirmed that more than 20% of the aluminium and phosphorus in the reagents was left in the mother-liquor as synthesis waste. For $AlPO_4$-5 to be produced on a commercial scale, the synthesis waste must be recovered for re-use or subjected to costly waste-water treatment before discharge, since the untreated effluent would be detrimental to the environment. As a valuable molecular sieve, it is worthwhile optimising the synthesis of $AlPO_4$-5, but studies on the stoichiometric synthesis of $AlPO_4$-5 aimed at minimising synthesis waste have, as yet, not been reported.

This work reports the stoichiometric synthesis of $AlPO_4$-5, aimed at minimising the residue from the hydrothermal synthesis, and its characterization by XRD, SEM, XRF, TGA and FTIR. The aim of this work was to explore the range of gel compositions from which the stoichiometric synthesis of $AlPO_4$-5 could be achieved, *i.e.* to convert the reagents wholly to $AlPO_4$-5, and hence leave no aluminium or phosphorus in the mother liquor. The approach adopted here was to minimise the amount of water used in the process.

Experimental

In the synthesis of $AlPO_4$-5 in this study the following gel compositions were used: $R:Al_2O_3:P_2O_5:xH_2O$, where x=10, 20 or 30, and R is the organic templating agent. The 'typical' gel composition: $R:Al_2O_3:P_2O_5:40H_2O$ was also employed. Three templating agents were explored: tetraethylammonium hydroxide (PRAC., 40% water solution, Fluka), triethylamine (99.9%, BDH, GPR) and tetraethylammonium bromide (Lancaster, 98+%). The other reagents were pseudoboehmite (73% Al_2O_3, VERSAL 900, La Roche Chemical), orthophosphoric acid (w/w. 85% solution in water, Aldrich) and distilled water. The syntheses were carried out in Teflon-lined stainless steel autoclaves (volume 18 ml) at 200 °C under autogeneous pressure. The synthesis conditions for representative samples are listed in Table 1.

Results and discussion

The XRD results for all samples are summarised in Table 1. The XRD analysis shows that all the samples synthesized using triethylamine as template were $AlPO_4$-5 with no evidence for impurities.[5] For example, Fig. 1 shows the XRD pattern for sample **1e**.

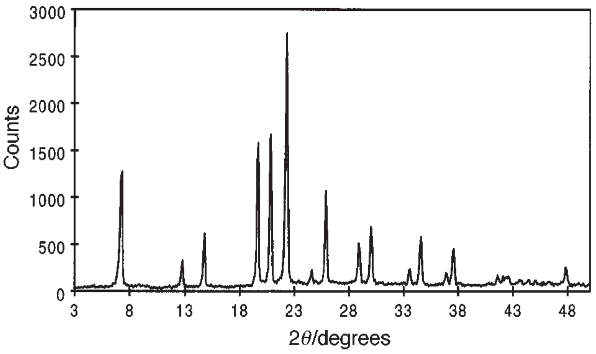

Fig. 1 XRD pattern for sample 1e.

XRD analysis also showed that at 200 °C, with tetraethylammonium bromide as template and for the molar gel composition: $TEABr:Al_2O_3:P_2O_5:xH_2O$, where x=10 and 20, the synthesis of $AlPO_4$-5 failed. This was probably due to the very low initial pH in the gels. When tetraethylammonium hydroxide was used as template and with molar compositions: TEAOH:

Green Context

The use of heterogeneous catalysts represents a major technology for minimising waste by simplifying recovery of catalyst and product isolation. However, the production of the catalyst too must be considered as a step towards a full life cycle analysis of the process as a whole. This paper addresses the clean production of a heterogeneous catalyst and shows how, with proper optimisation, catalysts can be prepared with minimal waste generation. ***DJM***

Table 1 Synthesis conditions, XRD results, % conversion to product of the reagents and aluminium:phosphorus ratio in the samples 'as synthesized', using ICP

Sample	Starting gel composition[a]	Crystalisation time[b]/h	Product (XRD)	Conversion (wt.%) Al	P	Al:P mol ratio in the products determined from the mother-liquor (ICP)
1a	$R:Al_2O_3:P_2O_5:10H_2O$	3	$AlPO_4$-5	94.4	88.7	100 : 094
1b		4	$AlPO_4$-5	91.5	85.3	100 : 094
1c		5	$AlPO_4$-5	98.1	94.2	100 : 096
1d		20	$AlPO_4$-5	99.3	94.6	100 : 096
1e		24	$AlPO_4$-5	99.6	96.8	100 : 097
1f		44	$AlPO_4$-5	98.3	93.0	100 : 095
1g		48	$AlPO_4$-5	97.1	92.3	100 : 095
2a	$R:Al_2O_3:P_2O_5:20H_2O$	3	$AlPO_4$-5	91.7	85.9	100 : 094
2b		4	$AlPO_4$-5	92.4	84.6	100 : 092
2c		5	$AlPO_4$-5	95.5	89.7	100 : 094
2d		20	$AlPO_4$-5	97.9	92.8	100 : 095
2e		24	$AlPO_4$-5	96.5	91.7	100 : 095
2f		44	$AlPO_4$-5	99.6	94.6	100 : 095
2g		48	$AlPO_4$-5	99.3	94.6	100 : 096
3a	$R:Al_2O_3:P_2O_5:30H_2O$	3	$AlPO_4$-5	75.2	60.9	100 : 081
3b		4	$AlPO_4$-5	81.2	70.9	100 : 087
3c		5	$AlPO_4$-5	88.9	79.0	100 : 090
4a	$R:Al_2O_3:P_2O_5:40H_2O$	3	$AlPO_4$-5	73.5	61.6	100 : 085
4b		4	$AlPO_4$-5	83.5	72.3	100 : 087
4c		5	$AlPO_4$-5	84.5	75.2	100 : 089

$Al_2O_3:P_2O_5:xH_2O$, where x=30 and 40, the product was mainly $AlPO_4$-5 mixed with impurities.

Table 1 also lists the percentage conversions to product of the reagents and the aluminium:phosphorus ratio in the synthesized samples, which were obtained by ICP analysis of the respective mother-liquors. The gel composition: $(CH_3CH_2)_3N:Al_2O_3:P_2O_5:10H_2O$ produced the highest conversion rate and the best aluminium:phosphorus ratio. At this optimal gel composition, the conversion rate and the aluminium:phosphorus ratio also depend on the crystallisation time. Only *ca.* 5% of the reagents remained in the mother-liquor as synthesis waste after a crystallization time of 5 h. When the crystallization time was 24 h, almost all the aluminium and phosphorus in the reagents had been converted into the desired product, however, even longer crystallization times tended to reduce the percentage conversion and the aluminium:phosphorus ratio. When the conventional composition incorporating $40H_2O$ was used, it was found that >20% of the reagents were left in the mother-liquor as synthesis waste. It can also be seen in Table 1 that the aluminium:phosphorus ratio for samples synthesized with 10 H_2O was much nearer the ideal of 1:1 than those synthesized with 30 or 40 H_2O.

Table 2 Chemical formulae of final products according to XRF and TGA

Sample	Chemical formula $Al_2O_3:P_2O_5:R:H_2O$	LOI (wt.%) (from TGA)
1a	1.00 : 0.97 : 0.24 : 0.59	13.2
1b	1.00 : 0.95 : 0.26 : 0.56	13.2
1c	1.00 : 0.96 : 0.25 : 0.56	12.9
1d	1.00 : 0.95 : 0.24 : 0.66	13.4
1e	1.00 : 0.95 : 0.24 : 0.71	13.6
1f	1.00 : 0.97 : 0.24 : 0.50	12.6
1g	1.00 : 0.96 : 0.23 : 0.39	11.8
2a	1.00 : 0.97 : 0.23 : 0.95	14.3
2b	1.00 : 0.93 : 0.24 : 0.74	13.7
2c	1.00 : 0.90 : 0.23 : 0.65	13.0
2d	1.00 : 0.98 : 0.25 : 0.76	13.5
2e	1.00 : 0.95 : 0.25 : 0.66	13.4
2f	1.00 : 0.96 : 0.25 : 0.43	12.0
2g	1.00 : 0.97 : 0.25 : 0.37	11.4
3a	1.00 : 0.84 : 0.21 : 1.46	17.1
3b	1.00 : 0.90 : 0.21 : 1.27	15.9
3c	1.00 : 0.89 : 0.22 : 0.99	14.4
4a	1.00 : 0.88 : 0.22 : 1.19	16.0
4b	1.00 : 0.90 : 0.21 : 1.16	15.6
4c	1.00 : 0.92 : 0.22 : 0.92	14.1

R = Triethylamine; $(CH_3CH_2)_3N$.

Table 2 lists the chemical formulae of all the products, obtained by XRF and by TGA. It can be seen that for samples **1a**–**2g**, the aluminium:phosphorus ratio in the product was close to the ideal 1:1, but for samples **3a**–**4c** it was nearer 1:0.90. These results suggested that by using the gel composition with 10 and 20 H_2O proposed here, the synthesis waste could be reduced compared with that using the 'typical' composition with 40 H_2O, and this suggestion was borne out by the ICP results listed in Table 1. The aluminium:phosphorus molar ratios in Table 1, calculated from their respective mother liquors, and those in Table 2, determined for the products by XRF and TGA, agree very closely and give further support to the results and accuracy of the analytical measurements. A point of interest is that the products from gel compositions with a high water content gave high LOI (35 to 800 °C) values, showing that excess water was occluded on the $AlPO_4$-5 framework. It has been shown previously[6] that excess water in contact with aluminophosphate frameworks tends to lead to hydrolysis and subsequent breakdown of the framework. It is therefore anticipated that the $AlPO_4$-5 produced from systems with restricted water may have a longer shelf life. Experiments are in progress to confirm this.

In the TGA for all samples, three distinct regions of weight loss were observed between 35 and 800 °C. The maximal loss for the first peak was in the range 67–103 °C, due to the loss of water which had filled the channels in the structure during the synthesis. The second peak around 200 °C and the third peak in the range 420–480 °C were both attributed to the loss of triethylamine.[7–8]

To summarize, the stoichiometric synthesis of the molecular sieve $AlPO_4$-5 has been accomplished at 200 °C using a gel of the new molar composition: $(CH_3CH_2)_3N:Al_2O_3:P_2O_5:10H_2O$. Under optimal conditions virtually 100% conversion was achieved.

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