Green Chemistry

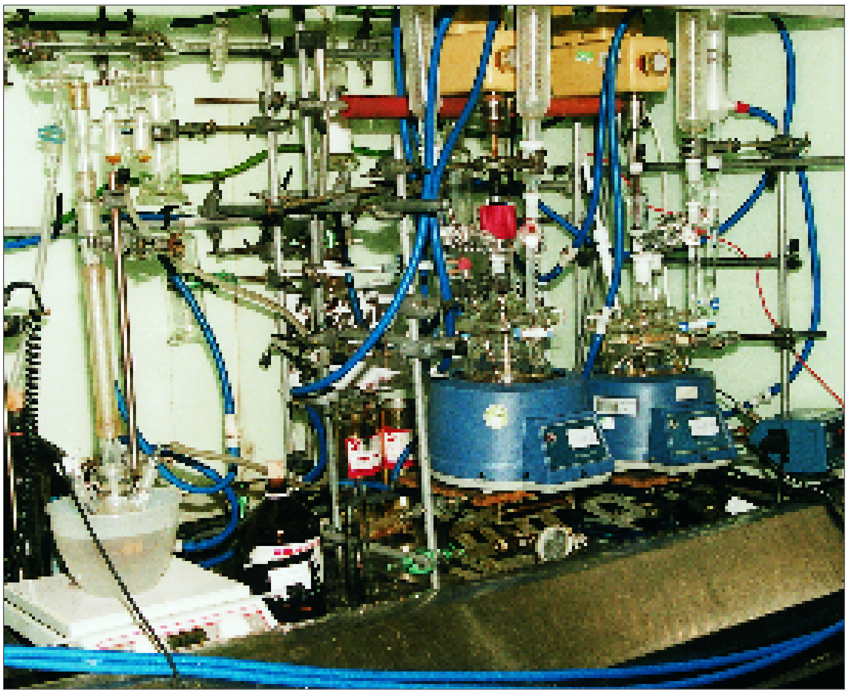
# Editorial

I am delighted to be able to welcome Jim Bashkin to the *Green Chemistry* editorial team as our Associate Editor for the Americas. Jim has considerable industrial and academic experience of environmentally benign chemistry and of educational development, and won one of the1998 Presidential Green Chemistry Challenge Awards. He is currently based at Washington University, St Louis, Missouri, USA.

In the front section of this issue Jim has an article on 'taking green chemistry from laboratory to chemical plant'(see p. G41) in which he describes the new commercial route to 4-aminodiphenylamine based on nucleophilic substitution for hydrogen. This is an excellent example of a successful nucleophilic aromatic substitution reaction that does not involve dehalogenation. Traditional chemistry of this type involves the introduction into an aromatic nucleus of a halogen which is subsequently displaced. Thus all of the halogen ends up as waste, typically in the form of salt (the problem is made worse by any waste produced in the initial halogenation stage, *e.g.* hydrogen halide). Of course, halogenation is more commonly used to introduce useful properties as a substituent in the final product and there is considerable scope for improving the efficiency of and reducing the waste from halogenation processes (see the article by Smith *et al*., p. 83).

Bashkin's article should encourage us to think of greener reaction chemistry not only in terms of better catalysis, solvent substitution and new techniques but also in terms of the synthetic route. The established routes that we learn about from text books and practice as students in the teaching laboratory are not necessarily the best—especially in these environmentally-conscious days!

If the production of a chemical product is environmentally unacceptable because of the nature or quantity of waste generated then we should first consider if we need to make that particular product (product substitution), then consider the route (alternative routes) and



then seek the best conditions for maximum efficiency in the selected route. Product substitution is likely to play an increasingly important role in green chemistry. As we are carried along by the euphoria of the approaching new millennium it is perhaps sobering to realise that fossil fuel-based hydrocarbon feedstock will cease to be the major raw material for the chemical and allied industries long before the end of its first century. The good news is that we can grow enough to provide the raw materials for these industries. The challenge is to make effective use of the molecules that nature provides us with in crops and to develop new products based on these. This will certainly lead to a considerable level of product substitution. One less direct environmental benefit of using crop-derived feedstocks is that while we currently invest considerable energy and generate considerable waste in oxidising hydrocarbons so as to give them functionality, the building blocks of the future already have high oxygen content, courtesy of nature! As with halogenation, oxidation in the future will largely be carried out so as to introduce specific functionality in the product rather than to facilitate its synthesis. Alternative feedstocks is the subject of a review (p. 107) and an article about an on-going initiative (p. G39). I look forward to seeing more articles for *Green Chemistry* on both sustainable feedstocks and product substitution.

**James Clark**, York, March 1999

*Several companies are developing new cleaner fuels*

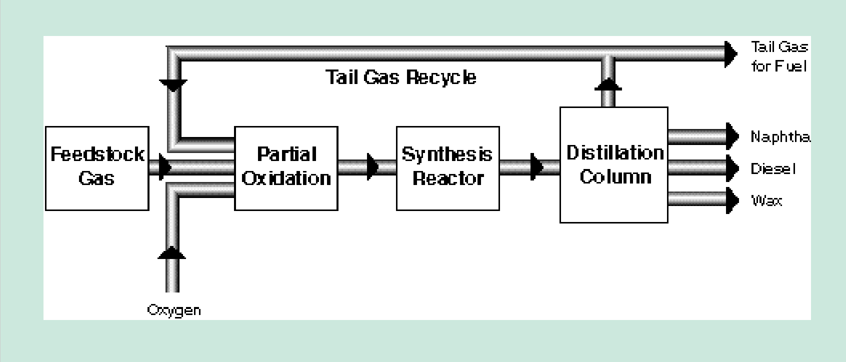
# Cleaner fuels

As controls on exhaust emissions are becoming tighter, producers are meeting the challenge to develop cleaner fuels.

***Elf***
Elf has launched a new fuel *(Europe Environment*, 530 p II.4) which is claimed to reduce emissions by up to 25%, as well as reduce fuel consumption by up to 5%.

***Shell***
Shell has launched an improved diesel *(Shell UK Focus 10, 27)* which has a sulfur content at least 90% lower than standard diesel and produces fewer particulates and less smoke.

***Rentech***
Rentech, based in Denver, Colorado, is currently promoting its patented technology, which it claims produces fuels which exceed all current and proposed US federal and state diesel emission requirements. The process is based on Fischer-Tropsch technology, which does not involve sulfur, making the fuels sulfur-free. Furthermore, the fuels produced contain no aromatics (making them devoid of carcinogens), burn with 80-90% less smoke than other diesels and emit less CO and NOx.
For more information see http://www.gastoliquids.com.

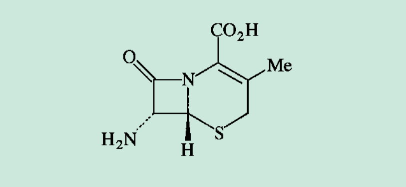


*The Rentech gas-to-liquids process*

***BP Amoco***
BP Amoco has announced that its service stations in the UK are to be the first in its worldwide network to move to selling an ultra-low-sulfur diesel. The new fuel, already available at 75% of the company's 1600 sites across Britain will soon be available to the remainder. BP Greener Diesel, as the fuel is known, emits 90% less sulfur dioxide and nearly a third less particulates and black smoke than standard diesel. This is the first phase of a much larger investment which the company plans over the next 6 years to produce a range of cleaner fuels that maximise performance but minimise exhaust emissions.

***A high-activity HDS catalyst for diesel fuel***
Cosmo Oil and Petroleum Energy Center (PEC) have developed a new hydrodesulfurization (HDS) catalyst of high activity, C-603A, to produce clean diesel fuel, whose sulfur content is less than 0.05 mass %. The preparation of this catalyst combines the use of zeolite technology and impregnation technology to provide excellent HDS activity [*Catalysis Today* **45**(1-4), 307-312]. C-603A possesses significantly higher activity than conventional Co-Mo/alumina catalysts. Industrial operation with this catalyst has successfully proven its high performance.

# New industrial processes



***7-ADCA***
DSM will be commissioning its new 7-ADCA (7-aminodeacetoxy-cephalosporinic acid) plant at Delft at the end of 2000. The new facility, which will create several dozen new jobs, will manufacture this semisynthetic antibiotic raw material using a new green process involving genetically modified strains of *Penicillium.* According to the company this innovation will substantially reduce the cost of production, cutting energy consumption by 35%, doing away with the need for toluene (30 tonnes/year), and reducing the use of other solvents from 25 tonnes/year to just several kg/year. The new facility will have a capacity of several 100 tonnes/year,

which is roughly the same as DSM's existing 7-ADCA unit; this will eventually be used for other purposes. For further information see http://www.dsmr.com.

***Ethyl acetate***

A team from the Qingdao Institute of Chemical Technology in China has developed a novel process for the production of ethyl acetate from ethanol and acetic acid. In this process, sulfuric acid is replaced by zeolite H-ZSM5. Despite the fact that the conversion is slightly lower than with the conventional process, the new route reduces waste, and corrosion to plant is also less, extending plant lifetime (*Xiangdai Huagong* **18**(11), 49).

***VAM***

BP Amoco has announced a new technology (called LEAP) which is being used to produce Vinyl Acetate Monomer (VAM). The new process involves the same raw materials—acetic acid, ethylene and oxygen as the current process. However, the benefits derive from advanced reactor design and process engineering. The new system relies on a fluidised bed reactor incorporating new reactor and catalyst design, and allows substantial downsizing of the plant. The new plant will be situated at the company’s site in Hull, UK, and will be commissioned at the end of 2000. Production volumes will be 250 000 tonnes/year. For further information see http://www.bpamoco.com. and for an article on the impact of the intensive processing on green chemistry see *Green Chemistry* **1**(1), G15-G17.

***Pigment intermediate***

Wakayama Seika Kogyo, a Japanese manufacturer, has announced a new process for the preparation of its dichlodine-H yellow pigment intermediate. The technique produces the pigment with a drainage volume of virtually zero while reducing the output of wastes to 40%. Global demand for the final pigment is *ca.* 20,000 tonnes/year. 3 Bn Yen will be invested in the new technology at its Kainan site in Wakayama Prefecture. The first material is due to be produced in 2000 [*Japan Chemical Week* **39**(2004), 3].

***Potassium dithiocarbamate-derived oil additives***

A newly developed clean technology developed at the National Ukrainian Academy of Sciences at Kiev for production of a highly pure potassium dithiocarbamate additive (used as oxidation inhibitor in lubricating oils) consists of synthesis of 3-aminothiolane-1,1-dioxide from butadiene, sulfur dioxide and ammonia in isopropanol (yield 85 to 90% by butadiene mass) and subsequent conversion of the resulted amine with hydrogen sulfide and potassium hydroxide in water-ethanol medium at 30 to 40°C for 3.5 h to potassium (1,1-dioxothiolan-3-yl)dithiocarbamate (yield 80.8% by amine mass) and potassium ethylxanthogenate by-product. Neither wastewaters nor solid wastes were formed. The process has been implemented in a commercial plant (capacity 150 tonnes/year) (*Khim. Tekhnol. Topl. Masel* **4**, 19-20).

# Renewable resources

### *Cyanobacteria as producers of molecular hydrogen—a clean and renewable energy source*

Hydrogen is a potential renewable replacement for fossil fuels. An attractive possibility is the direct splitting of water for generation of $H_2$ using solar radiation. This splitting can be achieved either in photochemical fuel cells, or by applying photovoltaics which directly utilizes solar radiation for electrolysis of water into $H_2$ and $O_2$. The third and most challenging option, according to Dr Peter Lindblad (Department of Physiological Botany, Uppsala University, Sweden), is the production of hydrogen by photosynthetic microorganisms. For photobiological $H_2$ production, cyanobacteria are among the ideal candidates since they have minimal nutritional requirements. They can thrive on air ($N_2$ and $CO_2$), water (electrons and reductant), and mineral salts with light as the only energy source. Cultivation is therefore simple and relatively inexpensive. In $N_2$-fixing cyanobacteria, $H_2$ is mainly produced by nitrogenases, but its partial consumption is quickly catalyzed by a unidirectional uptake hydrogenase. In addition, a bidirectional (reversible) enzyme may also oxidize some of the molecular hydrogen. Filamentous cyanobacteria have been used in bioreactors for the photobiological conversion of water to hydrogen. However, the conversion efficiencies achieved are low because the net $H_2$ production is the result of $H_2$ evolution via a nitrogenase and $H_2$ consumption mainly *via* an uptake hydrogenase. In order to achieve significant $H_2$ production rates over long time the following need to be considered:

- the strains used must be selected for their specific hydrogen metabolism.
- the selected strains must be genetically engineered in order to produce large amounts of $H_2$ (*e.g.* to increase the $H_2$ evolution by nitrogenase and/or by the bidirectional hydrogenase as well as through the production of mutants deficient in $H_2$ uptake activity).
- the overall conditions for cultivation in bioreactors must be improved.

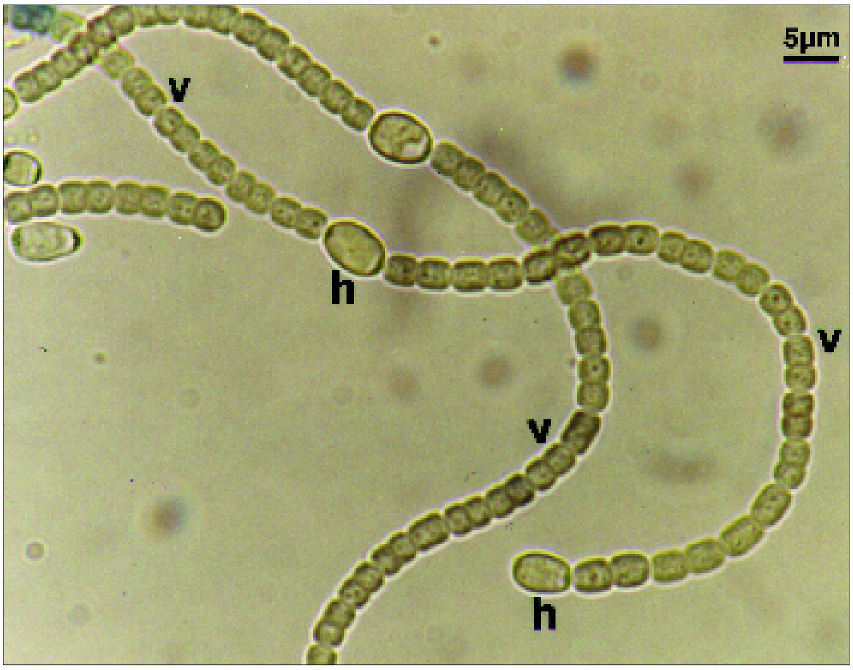


Photo: Peter Lindblad, Uppsala University.

*Filaments of the nitrogen-fixing cyanobacterium Nostoc 73102 forming heterocysts (h; site of nitrogen fixation) and vegetative cells (v; harbouring a complete photosynthesis)*

Symbiotic cells are of fundamental interest since they *in situ* 'function as a bioreactor'—high metabolism, transfer of metabolite(s) from symbiont to host ('bioreactor'), but almost no growth. Moreover, international coordination is necessary and at present two major initiatives can be recognized:

- IEA (http://www.iea.org) Agreement of the Production and Utilization of Hydrogen, Annex 14.
- COST 8.18 (continues as COST 8.41) (http://www.cordis.lu/cost/).

More information see:
Hansel A. and Lindblad P. (1998) Mini-Review: Towards optimization of cyanobacteria as biotechnologically relevant producers of molecular hydrogen, a clean and renewable energy source. (*Applied Microbiology and Biotechnology* **50**, 153-160) and http://www.fysbot.uu.se/fysbot/Cyano/Cyanomain5.html

***Wheat-based concrete***

Lightweight concrete products such as exterior panels for high-rise office buildings may soon be made with an unusual ingredient—wheat starch. The Agricultural Research Service (ARS), chief research agency of the U.S. Department of Agriculture, and Artlo Industries, Inc., of Perris, California, have entered into a Cooperative Research and Development Agreement today in Washington, D.C., to develop, test and commercialize wheat-based concrete. Artlo Industries provides concrete products for some of the world's largest construction corporations as well as for other architectural, design, and engineering firms. Under the new agreement, ARS scientists in Albany, California, will provide samples of wheat-based aggregate for making the concrete to Artlo Industries. Artlo Industries will test various mixes of the concrete for strength and durability, and will also determine cost-effective ways to manufacture lightweight, pre-cast wheat starch-based concrete products for indoor and outdoor uses. At the ARS Western Regional Research Center in Albany plant physiologist Gregory Glenn will help develop specifications for commercial products. Glenn holds a patent for wheat-based concretes.

*For further information contact: Martha B. Steinbock, Technology Transfer Coordinator, Pacific West Area, Agricultural Research Service, USDA, 800 Buchanan St., Albany, CA 94710, USA. Tel. (510) 559-5641, Fax (510) 559-5963, E-mail msteinbock@pw.usda.gov*

*Scientists at the U.S. Department of Agriculture have developed wheat-based concrete*

## Monsanto stops Biopol project

With the Biopol project, Monsanto has been working on the twin objectives of delivering low-cost polymer in plants through biotechnology and winning acceptance in the market for the compostable materials based on renewable resources. Today this product is being produced through fermentation technology acquired with the purchase of the Biopol business from Zeneca in 1996. Though significantly below today's costs for biodegradable polymers, the cost of Biopol production is still estimated to be 25-50% higher than conventional commodity polymers, such as polyethylene and polypropylene. Moreover the earliest time to market is 2005. This expected cost premium of the future product and the length of time to commercialisation has limited large-scale conversion away from conventional polymers to Biopol. Facing these challenges, Monsanto have over the past year sought a strategic alliance or investment partner to participate in further development of Biopol. It is as a result of failing to find such a partner that Monsanto have decided to stop the Biopol project.

# The greening of engineering

### Sue Haile[1] the Environmental Co-ordinator at the University of Newcastle-upon-Tyne, UK, discusses the green engineer

Ask any school child which colour they associate with engineering and they will inevitably say grey or brown, certainly not green. The concept of the chemical engineer as a net polluter is often still an integral part of public perception and one which needs to be addressed, particularly with the growing world awareness and concern for environmental issues.

In fact the chemical industry is deeply concerned with reducing its environmental impact and has been at the forefront of initiative development. For example the Responsible Care programme, originally set up in 1989 is an international chemical industry voluntary initiative designed to improve the performance of the chemical industry in the fields of health, safety and environment (Chemical Industries Association, 1992).

Future predictions of world scenarios invariably foretell increased population, increased economic development and extrapolated associated pollution loads upon the planet. It will fall largely to the engineering profession to come up with the means of continuing to produce the goods and services society requires whilst reducing the net output of pollutant per unit of product.

## Why the environment?

The advantages to industry of implementing environmental improvements are often quoted although there is still much reluctance, particularly on the part of smaller companies to tackle the issue.

Many companies world-wide are going further than this and are seeking formal recognition of their achievements by applying for accreditation to one of the environmental management standards such as the International Standard BS EN ISO14001 or EMAS, the Eco Management and Audit Scheme (93/1836/EEC) the European Environmental Standard. Those companies that are taking a positive attitude towards the environment are also demanding the same high standards from their suppliers and thus the pressure is pushed on down the supply chain. For example Volvo in Sweden recently asked 850 of their suppliers for a copy of their environmental policy.

Reasons given by industry for initiating environmental management schemes include the need to ensure current and future compliance with legislation—there are currently 400 EC draft or established regulations dealing with environmental topics!

By being proactive and taking an anticipatory approach companies may give themselves market edge and find new market opportunities. The value of the market for new environmental services and technologies has been estimated as in excess of $3.5 billion dollars world-wide and is predicted to grow to $640 billion by 2010 (Environment Council, 1998).

Financial savings are also an invariable result of improved environmental management either through reduced costs for raw materials, utilities, waste disposal or being cynical, in reduced fines for

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[1] Dr Haile is Course Director of the MSc course in Clean Technology at the Department of Chemical and Process Engineering at the University of Newcastle-upon-Tyne

## Why the environment?

**Requirements for Environmental Management Certification**
**Compliance with increasing legislation**
**Cost saving on raw material, utilities, waste disposal and treatment**
**Pressure from the public and stake holders**
**Increased legal liability**
**Environmental impairment insurance requirements**
**Market advantage and opportunities**
**Supply chain pressure**

non-compliance. Figures of 10% reduction in cost savings for companies during the first year of an environmental action are well documented, and often result from simple good housekeeping measures. The UK Environment Council estimates that a £70 saving per employee could be made by adopting simple resource-conserving strategies.

## Clean technologies

Recently much has been made of the move away from traditional 'end of pipe' solutions and the drive towards clean technology, a rather definitive concept with the target of zero emissions, and of cleaner production techniques, which are a comparative improvement on current technologies. Implementation of clean technology usually involves product modification such as changes in raw materials or processing improvements by, for example, process intensification.

Lower down in the hierarchy of environmental improvement methodology comes waste minimisation, which should not be disregarded as it is frequently achievable at zero cost through 'good housekeeping' or improved monitoring and targeting.

Cleaner production techniques are concerned with the concept of getting more value and use from a product or service with less resulting environmental impact. Some so-called 'green' products have been traditionally criticised as giving less from less, (*e.g.* a 'green' washing product which doesn't wash as clean).

## Techniques

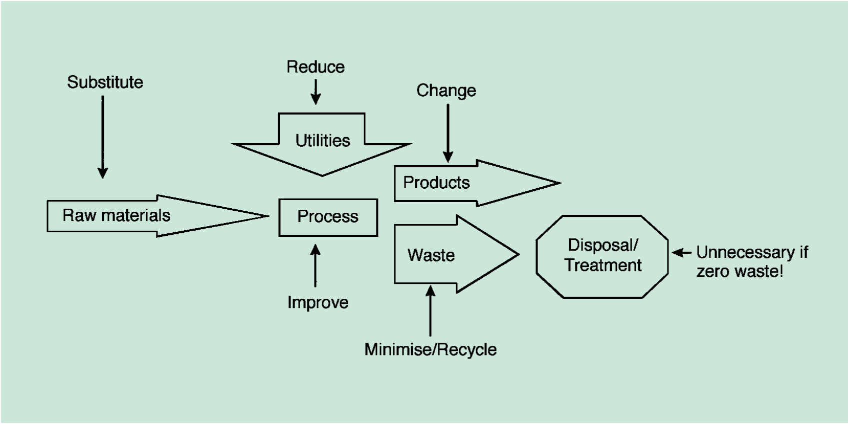
Four approaches may be mentioned in the identification of a cleaner technology although these are not definitive but are given as examples.

***'Natural Step'***
Devised by Dr. Karl-Henrik Robèrt in 1988 this approach is based upon society striving to operate according to four basic rules which should not be broken (Robèrt *et al.*, 1997). Implemented throughout Sweden, with every household being given a copy! The principles are used by IKEA a major international company in the day-to-day planning and running of their operations.

***ENVOP***
Developed in 1993 by BP/Costain, using a similar methodology to Hazop (Potter and Isalski, 1993). Env(*ironmental*) Op(*timisation*) involves a systematic review of a process driven by key words wherein a team of specialists familiar with the process plant ask at each step what would be the effect of certain changes to the operation of the plant. Key words used for example include raised or lowered temperature, pressure, flow rate, recycled water, *etc.* At each stage the question is asked as to whether this would improve the environmental performance without compromising production. The desired environmental improvements are categorised with the following six areas:

- Vapour emission reduction
- Liquid emissions reduction
- Solid disposal reduction
- Utility consumption reduction
- Noise reduction
- Reduction of odiferous discharges

The procedure then results in the compilation of list of potential changes to the production process and an assessment of the relative environmental benefits or drawbacks in each of the six areas listed above. This is then followed by a cost benefit analysis of the suggested options.



*Clean technology opportunities can apply to all stages in the life cycle*

## Principles of Natural Step

- **Substances extracted from the earth's crust must not systematically increase in nature.**

***We should not extract fossil fuels, and metals from the Earth's crust at a faster rate than they are replenished. We need to decrease the use of fossil fuels and reduce mining, recycle oils and metals*** **etc.**

- **Substances produced by society must not systematically increase in nature.**

***Substances should not be produced at a faster rate than they are broken down. We should phase out substances that cannot be biodegraded and are persistent in the environment*** **e.g.** ***PCBs.***

- **The physical basis for the productivity and diversity of nature must not be systematically deteriorated (diminished).**

***Don't use resources beyond the ability of sustainable development,*** **i.e.** ***so they are replenished at the same rate as their use. This for example will effect sustainable fisheries, forestry and agriculture.***

- **We must be efficient enough to meet all basic human needs or humans must achieve the just and efficient use of energy and other resources.**

***People must be able to meet their needs, (as opposed to their wants), and resources should be equally distributed.***

### *Life Cycle Assessment*

Life Cycle Assessment, (LCA), looks at each stage in a service or product life cycle from cradle to grave, (manufacture, use and disposal) and pinpoints areas of greatest environmental impact which may then be targeted for improvement. The process may also be used to compare the environmental burdens of two competing products. The concept has developed very rapidly in its application over the last decade and is widely used by companies such as Proctor and Gamble, (White *et al.*, 1995). It is now covered by an international standard (ISO14040).

LCA can be used to establish criteria for Eco-Labelling of products, to bolster the market of an existing product, to assess whether a proposed new product will produce a real environmental improvement, in product defence and to reduce the impact of an existing product.

LCA is a relatively new field but with great potential for growth and application although there are still relatively few practitioners.

### *Eco-Efficiency Fitness Compass*

The Eco-Efficiency Fitness Compass originated from Dow Chemicals in 1993, (ENDS, 1996). It consists of a six-point compass that allows comparison of a proposed product with an existing one based on consideration of six criteria. The compass uses six dimensions of eco-efficiency. Any new product is judged against the six criteria, based on achieving a maximum rating of 5. Existing products are given a hypothetical rating of two to enable the new product to achieve either a better or worse rating in comparison.

### Eco-efficiency criteria

- **Amount of energy used**
- **Amount of materials used**
- **Resource conservation**
- **Ecotoxicity**
- **Waste to landfill**
- **Durability and functionality**

## Conclusions

The approaches described vary in the stage in the production process in which they apply. The Natural Step is a philosophical approach relying on the four thermodynamic and ecological based rules. Industry should see adherence to these rules as the guiding light in the development of all of their operations.

ENVOP acts very much at processing stage once the product has already been decided upon.

LCA may be carried out on all or some stages in the life cycle of a product or service but should be concentrated where the environmental burden is felt to be the greatest. For example in a washing machine this would be in the 'use' phase, due to the water and energy requirements and resultant emissions. Whilst the concept is based on a 'cradle to grave' assessment of environmental impact, in practice the scope of the undertaking is often so vast that clearly defined system boundaries must be applied.

The Eco-Efficiency Fitness Compass essentially acts as a form of life cycle assessment but with the equivalent of LCA impact criteria being placed into one of six categories. It may be used to compare an existing product with a proposed one at the design stage or to compare two or more existing products.

Which tools are used to ensure less environmentally damaging products and services is a decision that should be made at the planning and design stage, although as we have seen methodologies exist that are applicable further along the production and processing chain.

The challenge to industry to meet the environmental requirements of the future has been issued. The engineering community has the tools and increasingly the expertise to ensure we are able to meet that challenge and will be at the forefront of the drive towards achieving sustainable development.

## References

BS EN ISO 14001. Environmental Management Systems: Specifications with Guidance for use, 1994.

BS ISO 14040 Life Cycle Assessment, General Principles and Practices, 1994.

Chemical Industries Association (1992). Responsible Care Management Systems, publication, CIA July 1992, ISBN 0 900 623 853.

Environment Council, Business and Environment Programme Handbook, October 1998, Background, p20.

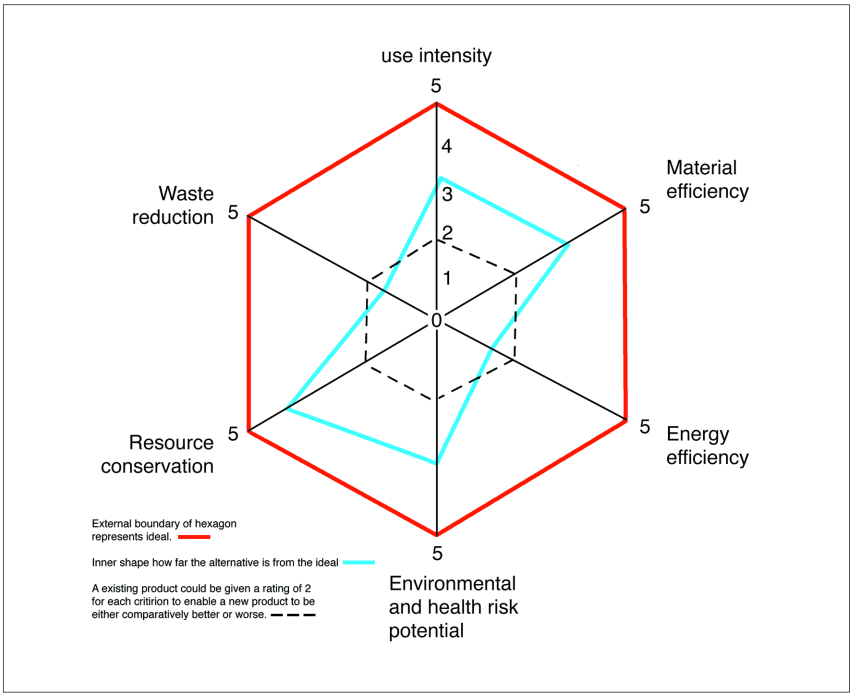
*Environmental Data Services (ENDS) Report 252*, January 1996, 16-19

European Commission 93/1836/EEC Regulation allowing voluntary participation by companies in the industrial sector in a community eco-management and audit scheme (OJ, L168 10 July 1993).

Potter, N.; Isalski, W. H. Environmental Optimisation, The ENVOP Technique, *Environmental Protection Bulletin,* 1993, **26**, 17.

Robert, K.-H.; Daly, H.; Hawkins, P.; Holmberg, J. *Journal of Sustainable Development and World Ecology*, 1997, **4**, 79-92.

White, P.; Franke, I.; Hindle, I. Integrated Solid Waste Management: A Lifecycle Inventory Publication, Chapman & Hall, 1994.



*The Eco-Efficiency Fitness Compass*

*The team at the Green Chemistry Network. Left to right: Helen Coombs, Mike Lancaster and James Clark*

# Green Chemistry Network

As you are probably aware The Royal Society of Chemistry announced last October that it was funding the establishment of a Green Chemistry Network (GCN) based at the University of York under the Directorship of James Clark. The full team is now in place at York with the appointment of Mike Lancaster as the Network Manager and Helen Coombs as part-time Administrative Assistant.

The aim of the GCN is to promote awareness and facilitate education, training and practice of Green Chemistry in industry, universities and schools. With this in mind we are in the final stages of putting together a Technical Advisory Panel (TAP) consisting of representatives of Trade Associations, Professional Organisations, Government Departments and Funding Bodies. The TAP will advise and hopefully contribute to the programmes and initiatives we develop. We are also busy recruiting network members, so please copy and fill in the registration form in the back of this issue. We are producing a database of network members highlighting areas of interest and expertise, and this will eventually be available to members on our GCN web site as well as in hard copy. The web site is currently being set up (hopefully it will be accessible within the next two months and will be hosted on the chemsoc.org site). So please pay us a visit and let us know how you would like to see this site developed.

As we only have a very small core of people working on network activities we need to rely heavily on member volunteers. We are keen to start working on providing educational material for schools and universities. If anyone out there has examples of processes or reactions suitable for use as simple experimental exercises which highlight green chemistry concepts please let us know. Still on the topic of education we have got together a series of articles on green chemistry for publication in *Chemistry Review* (Philip Allan Publishers, ISSN 0959 8464), we are now looking for people to write articles for the RSC magazine *Education in Chemistry* aimed at 'A' level and undergraduate students. If you have any suitable topics please get in touch (email: greennet@york.ac.uk).

'copy and fill in the GCN registration form at the back of this issue'

## Sustainable production and use of chemicals

The UK Royal Commission on Environmental Pollution (RCEP) has responded to the UK Department of the Environment, Transport and the Regions (DETR) consultation document on Sustainable Production and Use of Chemicals. In it the RCEP points out that it believes that the management of risks from new chemical substances is generally effective but that there is a need for an improved system for assessing the risks posed by chemical substances in use prior to 1981. In the Royal Commission's view, the solution lies in industry taking greater responsibility for the substances it produces and markets, subject to appropriate safeguards. This approach should build on the existing initiatives started by the UK's Chemical Industries Association (CIA) and legislation should reflect the greater responsibility taken by industry, aim for consistency between the regulations controlling different chemicals, and preserve accountability. It also points out that policies should have an international focus. In the context of self-assessment, the pursuit of greater eco-efficiency should play a very important role and it was noted that the CIA already has an agreement with the DETR on energy efficiency. For further information on this consultative document see the Feature Article on page G47 of this issue of *Green Chemistry.*

### *Chemicals in the European environment: low doses, high stakes?*

In the European Environment Agency (EEA) and United Nations Environment Programme (UNEP) Annual Message 2, the subject of Chemicals in the Environment is considered. The statements are aimed at raising public and political awareness on critical or emerging issues to facilitate preventative action by governments and others.

The EEA/UNEP survey reveals that we may face serious, if hard-to-identify risks, but also that measures to reduce these risks are available. The search for greater eco-efficiency in the production and use of chemicals is partly driven by concern over the possible effects on humans and ecology of many combinations of chemicals.

The weaknesses in present policies for managing chemicals in the EU will be clarified and addressed by the current European Commission review. The statement makes it clear that the aim must be to strike the right balance between different approaches to the risks of chemicals and to the benefits and costs of their use.

It is recognised that there is still great room for improvement since even the best chemical plants in Europe are still believed to be inefficient in their use of energy and in their production of wastes. The full text of the EEA/UNEP Annual Message 2 on the State of Europe's Environment can be viewed at http://www.eea.eu.int/document/brochure/chemicals/index.html.

## Industry uneasy about taxes

*Environmental taxes on energy and pesticides are under active consideration in Europe*

The European Union seems likely to introduce an energy tax in an effort to reduce carbon dioxide emissions. However, the chemical industry in Europe is very concerned about the effects such a tax would have on its global competitiveness. With energy costs in Europe already higher than those in the US and Asia, CEFIC (the European Chemical Industry Council) fears that such a tax could have a very negative impact on its members. However, Germany (currently holding the EU Presidency), France and the UK are considering energy taxes. A few industrialists, such as Rodney Chase, president of BP-Amoco, are in favour of energy tax, as a valid instrument in the drive for energy efficiency. Other proponents of the tax point to the possibility that the tax could be balanced by other incentives which would leave the overall tax burden essentially unchanged (*Chemistry and Industry*, 1999).

The UK Department of the Environment is also considering a pesticide tax (*Crops*, 1998, extra issue, 6). Such a tax is already in place in Denmark, where tax on insecticides is 56% and 33% on other agrochemicals. Additionally the Danes have banned several agrochemicals in common use in many other countries. The British Agrochemicals Association (BAA) is strongly opposed to the introduction of such pesticide taxes in the UK, and British farmers are worried about the consequences, with many farms already in a precarious economic situation. Many farmers may decide to bring every square metre of their land into full production to stay in business, reversing the great strides made in habitat creation and pollution control on farmland over the past 5 years. Environmental groups are generally in favour, seeing the revenues of such a tax potentially being available for environmental projects.

## Sustainable development in the OECD

Sustainable development was one of the five priority areas for future work of the OECD identified by the Secretary General. In the 1997 report of the high level advisory group on the environment, *Guiding the transition to sustainable development ; a critical role for the OECD,* it was noted that governmental policies on the environment and economic matters were not well connected and it was recommended that the OECD should become the leading international organisation analysing how best to harmonise policies in these areas. In response to this challenge the OECD has developed a strategy for work that should be undertaken up to the year 2001. This strategy has been endorsed by the OECD Ministers and it is intended that there will be major report to one of their meetings in 2001. A number of intermediate studies and reports will be produced in the interim and will be available on the OECD website (http://www.oecd.org/)

## Chemical testing programme to speed up

The US Chemical Manufacturers Association (CMA), along with the White House, the EPA and the Environmental Defense Fund has announced a major testing programme for 2800 industrial chemicals. These chemicals are all produced in quantities in excess of 1 Mlb/year [*Soap, Cosmetics, Chemical Specialities* 1998, **74**(12), 12]. This 6-year testing programme will investigate environmental fate, eco- and human toxicity, and is estimated to cost $700M. The programme is in response to the finding that the majority of chemicals produced worldwide (around 100,000) have not been subjected to a full risk assessment. Audits carried out in Europe have indicated that *ca*. 75% of the highest production volume chemicals do not have enough toxicity data for even a preliminary assessment to be made. This mirrors surveys carried out in the US. CEFIC (the European Chemical Industry Council) has agreed to the principle of a global voluntary initiative and will aim to produce a list of around 1000 priority chemicals, as well as contribute to a worldwide research programme (*European Chemical News - Chemscope*, 1998, 21-23).

*The EPA is conducting a major chemical testing programme*

In an additional measure, the CMA has initiated a five-year research programme, costing $100M, which is designed to examine the basic mechanisms of interaction of chemicals with the environment, rather than assess specific chemicals individually (*Chemistry and Industry*, 1999, 131). The major areas of the project can be divided into five themes—exposure assessment, risk measurement, carcinogenicity, respiratory toxicology and hormone disruption. Other themes are how chemicals affect the immune system, the nervous system, ecosystems and the atmosphere. The work will be based predominantly at the Chemical Industry Institute of Toxicology in California. Results will be disseminated on a website.

## New funding opportunity for water and watersheds research

A EPA/NSF/USDA Partnership for Environmental Research will provide grants for research on water and watersheds. Approximately $7 million will be awarded, with an award range of $100,000 to $300,000 per award per year and an approximate duration of 2-3 years. Applications may be made up to May 28, 1999 and awards will be made in early Fiscal Year 2000. Further information is available from the website: http://es.epa.gov/ncerqa/rfa/water.html. Additional information on this and other calls for proposals are available in HTML and PDF formats on the NCERQA Web site at http://es.epa.gov/ncerqa/

## The greening of government

The UK House of Commons Environmental Audit Committee has produced a report entitled ‘The Greening of Government’ which applauds sustainable development but regards achievements as being disappointing. It is the intention of the Committee to audit the governments green performance on the basis of annual departmental reports which should state what has been done in practical terms. The Chairman of the Committee, John Horam MP has stated that they would like to see a high profile debate in parliament on environmental matters, led by the Deputy Prime Minister. He recognises that environmental debates get driven by the big issues such as climate change and that targets for emissions cuts for example, can be over-ambitious. He pointed out that while the big issues need to be examined, so do the more immediate concerns of greening government (*Business Standards*, November 1998).

## IENICA

The Interactive European Network for Industrial Crops and their Applications, IENICA, is a project funded by DGXII of the European Commission. It has been running since 1997 under the coordination of Melvyn Askew at the Central Science Laboratory, Sand Hutton, York, UK. The project has 14 partners in the EC which includes all member states with the exception of Luxembourg, the project also has a new partner in Hungary and has close links with Poland.

***IENICA internet home page***
***http://www.csl.gov.uk/ienica***

The IENICA project has four targets:

- Establishment of an interactive network to promote industrial and scientific collaboration between science and industry and between member states.
- Preparation of individual state reports on potential / challenges / opportunities for industrial crops in individual member states and EU overall. This will be available during 1999.
- Development of an interactive database of industrial plants and products available free of charge on the internet at http://www.csl.gov.uk/ienica
- Three seminars for industry and research:

  - Natural Fibres Performance Forum—Needs, Challenges, Opportunities
    May 1999.
    Copenhagen, Denmark.

  - Vegetable Oils—Meeting the Needs of Industry.
    June 1999.
    Rotterdam, Netherlands.

  - Speciality Chemicals for the 21st Century.
    September 1999.
    Nice, France.

IENICA publishes a regular Newsletter with articles on European-wide developments in industrial crops; authors range from project partners to industry contacts to officers at the European Commission. We welcome suggestions for contributions from our readers. The newsletter also has information on forthcoming industrial crops events, including IENICA seminars. To receive copies of the newsletter or add your name to the mailing list, please contact s.hugo@csl.gov.uk.

IENICA launched its internet site in February 1998, it is accessed directly at http://www.csl.gov.uk/ienica. The website has a database of crops, information on forthcoming industrial crops events, and background details of the project.

The crops database provides information on a wide range of plants with novel applications in industry. Crops listed are, for example, those which yield alternatives to oils normally derived from the petrochemical industry for use as lubricants, fuels, plastics, detergents, paints; plants which can be used to provide energy when burned; plants which yield quality fibres which can substitute for carbon- or petrochemical-derived sources. There is also information on plants which are sources of therapeutic chemicals, dyes, carbohydrates, paper or pulp and traditional food crops for which non-traditional uses have been developed. Environmental benefits accrue from the use of these bio-renewable products.

Entries are described botanically and in terms of quality characteristics, constraints on production, market potential, crop production statistics, agronomy, pests and diseases, also useful contacts and links to EC funded projects

It is proving to be a useful tool to producers, end-users, industry and academia alike.

Another feature of the website is a ‘Contacts’ page where we have direct links with useful websites in UK, Europe and worldwide, including contacts with industry.

*For further information on the project or to submit information to the website please contact s.hugo@csl.gov.uk or telephone + 44 (0)1904 462259.*

## Chemical Education Foundation

The Chemical Education Foundation (CEF) has developed a range of publications and videos on chemical product stewardship, regulatory training and safe chemical handling. Many of these publications are free. The CEF was formally known as The Natural Association of Chemical Distributors Educational Foundation (NACDEF) and is a non-profit educational organisation that serves as a primary worldwide resource for educational outreach and training for businesses, communities and individuals served by the chemical industry.

The CEF website address is http://nacdef.com/ and the contact is Jennifer Aleknavage (Fax +1 703 527 7747).

*James Bashkin and his wife Shelley Shray with the 1994 Thomas and Hochwalt Award, which he shared with Michael Stern*

# James Bashkin—

## our Associate Editor for the Americas

James K. Bashkin was born in Iowa City, USA, in 1958, but spent most of his early years in Tucson, Arizona. After attending the University of Arizona for a year, he transferred to the University of California at Irvine. After graduating in 1977, he went to Oxford to do his graduate work with Malcolm L. H. Green. His graduate work involved primarily the structural and synthetic chemistry of molybdenocene dimers. He obtained a D. Phil. in organometallic chemistry in 1982, and then moved to R. H. Holm's group at Harvard, where he was an NIH postdoctoral fellow. In the Holm Group, he worked on synthetic models for the iron-molybdenum cofactor (FeMoco) of nitrogenase, iron thiololate species, and a soluble cobalt sulfide that contains the $Co_8S_6$ cluster unit found in the mineral pentlandite.

He then took a position at Monsanto, in the Chemical Sciences Department of Corporate Research. During this time (1985-91), he developed programs on solid-state reference electrodes, a new green chemistry version of nucleophilic aromatic substitution, and catalytic chemotherapy based on functional mimics of ribozymes. The green chemistry was recently commercialized in Europe by Flexsys; it is an example of nucleophilic aromatic substitution for hydrogen (NASH). Flexsys is a joint venture between Solutia (formerly Monsanto's chemical company) and Akzo Nobel. In 1994, Professor Bashkin and co-inventor M. K. Stern shared Monsanto's highest science and technology award, the Thomas and Hochwalt prize, for this chemistry, and in 1998, they and a group of colleagues received the President's Green Chemistry Challenge Award for Alternative Synthetic Pathways (http://www.epa.gov/opptintr/greenchemistry/past.htm). Professor Bashkin was appointed to the Editorial Advisory Board of *Chemical Reviews* in 1991, co-chaired the NSF Organometallic Workshop (1988-1990), and served on an NSF review panel for SBIR grants.

In 1991, Professor Bashkin joined the chemistry faculty at Washington University as an Assistant Professor. He has continued to pursue bio-organic and -inorganic approaches to catalytic drugs, and to study the mechanism of RNA transesterification and hydrolysis. In 1998, he guest-edited a thematic issue of *Chemical Reviews* on 'RNA/DNA Cleavage Chemistry', and contributed the article on ribozyme mimics. Professor Bashkin has published more than 45 papers and is an inventor on 6 U.S. patents. He has remained active in the green chemistry arena as a consultant for Flexsys and through a new program to broaden the scope of his original NASH reaction so that it can serve as a general method for halide-free bond formation.

Recently, Professor Jim Bashkin was chosen as one of 125 scientists and engineers world-wide to contribute to a document to help define environmentally sustainable technologies for the Institute for Prospective Technological Studies in Seville, an institute of the EC's Joint Research Centre. The final report is to be delivered to European Policy makers.

Information on Professor Bashkin's green chemistry research can be found at http://wunmr.wustl.edu/Faculty/Bashkin/jkbgreen.html. Contact information: Tel.+1 (314) 935-4801. Fax +1 (314) 935-4481.
Email: bashkin@wuchem.wustl.edu

# Taking green chemistry from laboratory to chemical plant

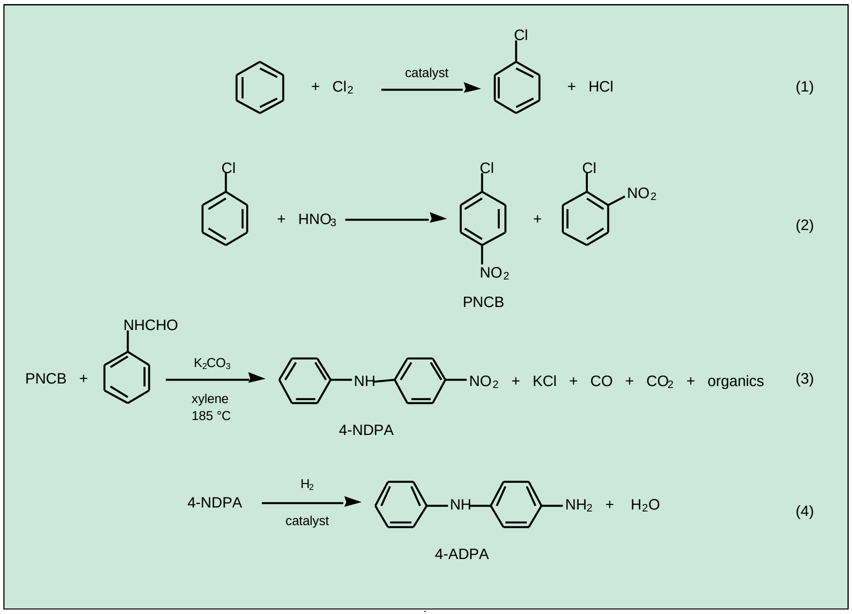
**James Bashkin, Roger Rains and Michael Stern give a personal perspective on developing a new route to 4-aminodiphenylamine (4-ADPA)**

Over the past several years, we and a team of talented colleagues have had the opportunity to follow a new green chemistry process from the stage of problem definition to initial laboratory discovery, through pilot-scale studies and on into commercial practice. The chemistry was initiated at Monsanto Company and finalized at Flexsys, with participation of Solutia in the latter stages. Here we describe how this work evolved, while offering some personal perspectives that may aid other chemists and engineers in the discovery and implementation of their own green chemistry.

*A green process has been developed for the synthesis of 4-ADPA, an important intermediate in the synthesis of antioxidants/antiozonants for automobile tyres*

## The traditional chemistry process for 4-ADPA synthesis

The chemistry previously employed by Monsanto to make ADPA involved the synthesis of 4-nitrodiphenylamine (4-NDPA) as shown in the following sequence of reactions:



The above chemistry requires *p*-nitrochlorobenzene (PNCB), which must be separated from its *ortho* isomer after synthesis. The *p*-chloro group is only introduced so that it can later be removed, to be discarded in an aqueous waste stream containing KCl.

## The green chemistry process for 4-ADPA synthesis

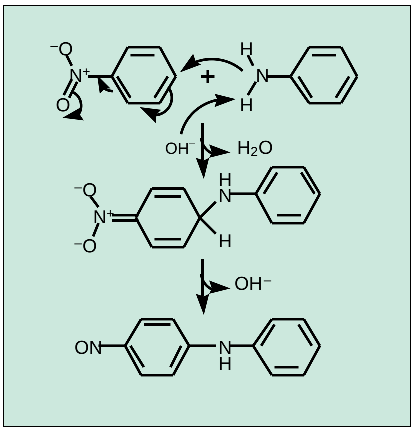
A new process was therefore developed with the objective of the dramatic reduction or elimination of as much inorganic, organic and aqueous waste as possible. We sought to reach this objective by eliminating the use of chlorobenzenes altogether, thereby avoiding any salt disposal issues.

Our process, which was designed to impact the rubber chemicals industry, is best described as nucleophilic substitution for hydrogen. One version of the key reaction is shown overleaf

### Starting Materials for 4-ADPA Synthesis

***Traditional chemistry***
**aniline**
**formic acid**
**nitrobenzene**
**chlorine**
**$K_2CO_3$ (consumed)**
**xylene (solvent for final step)**

***Green chemistry***
**aniline**
**nitrobenzene**
**tetramethylammonium hydroxide (reusable catalyst)**



The indicated (nitroso) compound is the predominant product formed and is subsequently hydrogenated to form 4-ADPA, an important intermediate in the synthesis of antioxidants/antiozonants for automobile tyres.

It turned out that the project was able to achieve its environmental goals and also reduce the total manufacturing cost of 4-ADPA enough to justify the decision to invest in the commercialization of a new chemical plant. This new chemical plant demonstrates the long-term commitment of Flexsys to the rubber chemicals business and has solved many of tomorrow's environmental problems.

## Success factors of the green chemistry approach

Certain features are unique to this project but others can be generally applied to the commercial development of new green chemistry.

> 'green chemistry is not solely process engineering – it can encompass entirely new chemical reactions'

- It was essential to know the appropriate chemical literature, but not to pay it too much homage. In fact, clues to our new chemistry were found in the literature from the turn of the century,[1,2] and inspiration came from the recent work of Stahly[3] and Makosza.[4,5] However, we found our success by defining the ideal result and working backwards rather than by collating what was known and attempting to rework it. The ideal result in this case was the simple and direct coupling of nitrobenzene and aniline, and this turned out to be the exact solution to the problem.

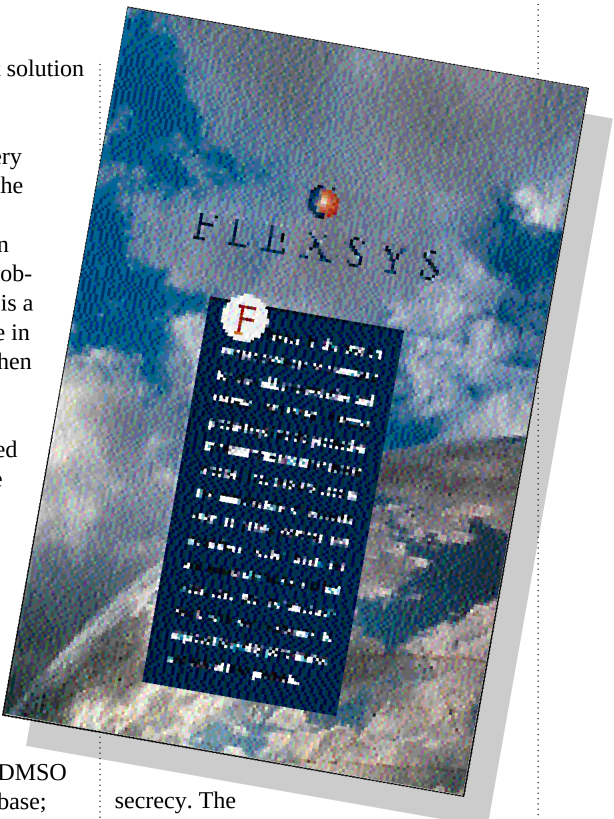
- It was essential that the discovery team did not insist on redefining the problem into one that was readily solved without regard for the main goals. Certainly, redefining the problem can be a valid strategy, but it is a luxury that is not always available in an industrial setting, especially when the chemical compound under investigation is already a well-defined product with an established sales base. This again can provide difficulty at the academic/industrial interface: in academics, a solution to *any* important problem is inherently valuable, while in industry, one is constrained to solve *the* current problem of actual commercial (and environmental) importance. For example, our initial laboratory success occurred with DMSO used as a solvent and NaH as the base; this demonstrated the concept of NASH chemistry applied to 4-ADPA synthesis, but would be impractical for an industrial process. In our interactions between discovery and production teams, it was helpful for the discovery teams to learn about the full manufacturing and business context of the problem, and the constraining parameters imposed by this context, during the process of formulating potentially new synthetic routes.

### Successes of the green 4-ADPA process

**In comparison to the process traditionally used to synthesize 4-ADPA, the Flexsys process generates 74% less organic waste, 99% less inorganic waste, and 97% less waste water.**

**In global terms, if just 30% of the world's capacity to produce 4-ADPA were converted to the Flexsys process, chemical waste would be reduced by 74 million lb./year and waste water would be reduced by 1.4 billion lb./year.**

- It was essential to have clear communication between those who best understood the nature of the waste problem and those who worked on discovering solutions to the problem. Potential problems that can derail or impede such communication are political or 'turf' considerations and issues of secrecy. The latter can be a particular stumbling block for academic/industrial collaborations, because it may be difficult for companies to reveal their largest environmental problems to outsiders. It may be helpful to note that all three present authors were employed at Monsanto Company when our project was started.



To be successful, it helped to have a team with a broad professional background, incorporating both experts in the field and scientists new to this area. We benefited from excellent coworkers in synthetic chemistry, physical and analytical sciences, and chemical engineering, and from invaluable management support. Of course, many of our coworkers appeared as coauthors of papers[6-10] and coinventors of patents.[11-21] The special contributions of Chi Chao Chieng, James M. Allman, Brian T. Kirtley, Frederick D. Hileman, Karen A. Andreshak, Ralph A. Genetti, and Larry C. McCune were also recognized by designating them as co-winners with ourselves of our Presidential Green Chemistry Challenge Award, administered by the United States Environmental Protection Agency (for more information on this important program, see http://www.epa.gov/opptintr/greenchemistry).

- The synergy of our team was essential to its success, as was the courage of management to commit the funds for a pilot plant and subsequent full-scale chemical plant. This required a successful crossing of many borders, initially within

Monsanto (MTC) central research and operating units and then between Monsanto and Akzo Nobel (AKZO) during the creation of Flexsys, a joint venture comprising the combined the rubber chemicals businesses of the two parent companies. To further complicate matters, Monsanto divested itself of its chemical business during the final stages of the project to create the new company, Solutia (SOI). It would have been easy for the program to fail simply due to complex and shifting alliances, but the importance of green chemistry and the combined financial and environmental benefits of the new process were kept clearly in mind by those involved. We are certainly grateful to all of our colleagues, named and un-named, who contributed to this process.

> ‘the enormous power of chemistry to do good (and make money) should not be overlooked’

## Conclusions

There are several aspects of this program that we hope will become general descriptors for the field of green chemistry.

- It is clearly possible to develop green chemistry that actually decreases associated process costs, even in the absence of any accounting for environmental costs.

- Green chemistry is not solely process engineering: it can encompass entirely new chemical reactions, discovered tomorrow, that were unknown today.

- As successful as traditional chemical synthesis has been in providing the reactions upon which today’s industry and modern society depend, there is ample room for new paradigms, even in seemingly simple bond-forming reactions.

- Excellent communication amongst research, process and business groups is vital for the continued development of relevant green chemistry.

- The enormous power of chemistry to do good (and make money) should not be overlooked amongst the flood of new technologies from other fields and the negative connotations sometimes associated with the ‘central science’.

Chemistry can prevent pollution, not just create or measure it, all while providing truly essential goods for modern society. Creative new chemistry and engineering are, we suspect, far less likely without strong industrial and academic research labs, and strong ties between them.

## References

1 A. Wohl and W. Aue, *Chem. Ber.*, 1901, **34**, 2442-2450.
2 A. Wohl, *Chem. Ber.*, 1903, **36**, 4135-4138.
3 G. P. Stahly and D. R. Bell, *J. Org. Chem.*, 1989, **54**, 2873-2877.
4 M. Makosza and A. Kwast, *J. Phys. Org. Chem.*, 1998, **11**, 341-349.
5 M. Makosza and K. Sienkiewicz, *J. Org. Chem.*, 1990, **55**, 4979.
6 M. K. Stern, F. D. Hileman, and J. K. Bashkin, *J. Am. Chem. Soc.*, 1992, **114**, 9237-9238.
7 M. K. Stern and B. K. Cheng, *J. Org. Chem.*, 1993, **58**, 6883-6888.
8 M. K. Stern, B. K. Cheng, F. D. Hileman, and J. M. Allman, *J. Org. Chem.*, 1994, **59**, 5627-5632.
9 M. K. Stern, B. K. Cheng, and J. Clark, *New J. Chem.*, 1996, **20**, 259-268.
10 J. K. Bashkin, ‘Benign Organic Synthesis’, Environmental Protection Agency document EPA/600/R-94/125, Cincinnati, Ohio, 1994.
11 M. K. Stern and J. K. Bashkin, Method of preparing 4-aminodiphenyl amine, U. S. Patent 5,117,063.
12 M. K. Stern and B. K. Cheng, Process for preparing N-aliphatic substituted *p*-phenylenediamines, U. S. Patent 5,252,737.
13 M. K. Stern and J. K. Bashkin, Process for preparing *p*-nitroaromatic amides and products thereof, U. S. Patent 5,331,099.
14 M. K. Stern and B. K. M. Cheng, Process for preparing *p*-nitroaromatic amides and products thereof, U. S. Patent 5,380,946.
15 M. K. Stern and B. K.-M. Cheng, Process for preparing substituted aromatic amines, U. S. Patent 5,382,691.
16 M. K. Stern and B. K. Cheng, Process for preparing *p*-nitroaromatic amides and products thereof, U. S. Patent 5,436,371.
17 M. K. Stern and J. K. Bashkin, Method of preparing 4-aminodiphenyl amine, U. S. Patent 5,453,541.
18 M. K. Stern and B. K.-M. Cheng, Process for preparing substituted aromatic azo compounds, U. S. Patent 5,552,531.
19 M. K. Stern, J. M. Allman, J. K. Bashkin, and R. K. Rains, Method of preparing 4-aminodiphenylamine, U.S. Patent 5,608,111.
20 M. K. Stern and B. K.-M. Cheng, Process for preparing substituted aromatic amines, U. S. Patent 05618979.
21 M. K. Stern and J. K. Bashkin, Method of preparing 4-aminodiphenyl amine, U. S. Patent 05623088.

## Biographies

**From 1985 to 1991 James Bashkin (Email:bashkin@wuchem.wustl.edu) worked for Monsanto and during that period he initiated programs on solid-state reference electrodes, a new green chemistry version of nucleophilic aromatic substitution, and catalytic drugs based on functional mimics of ribozymes. In 1991 he joined the chemistry faculty of Washington University in St Louis as an Assistant Professor.**

**Following a career of 27 years with Monsanto, Roger Rains (Email: rkrains@flexsys.com) joined Flexsys when it was created by Monsanto (now Solutia) and Akzo Nobel. he has been involved for many years in process development, process improvement, cost reduction and quality improvement from lab to pilot plant to commercial scale.**

**Michael Stern (Email: michael.k.stern@monsanto.com) joined Monsanto in 1988 and has been involved in a variety of research programmes relating to the development of novel chemical processes and pharmaceutical processes. He is currently Director of Technology and Senior Science Fellow within Monsanto's Agricultural Sector's Chemical Herbicide Business.**

**James Bashkin and Michael Stern were co-recipients of the Monsanto Thomas and Hochwalt Science and Technology Award in 1994 for their roles in the discovery of the aromatic substitution chemistry used in the development of Monsanto's new process to 4-ADPA.**

# New clean etherification

Methods to prepare ethers generally involve the use of strong acids or bases. For example, the classical Williamson synthesis involves alkoxides and alkyl halides, generating an equivalent of salt. Other routes involve strong acids to either protonate an alkene, which is captured by an alcohol, or to dehydrate an alcohol to give a carbocation, followed by reaction with an alcohol. In both cases the acid must be separated and neutralised, again leading to salt formation.

Chris Strauss and his research team at CSIRO Molecular Science in Clayton, Australia, have come up with a simple and elegant route to symmetrical ethers which avoids these harsh, waste-generating procedures (*Chem. Commun.*, 1999, 283). Their approach uses an alkyl halide as catalyst. The alkyl halide reacts with an alcohol molecule according to reaction 1, to give the ether and a molecule of HX

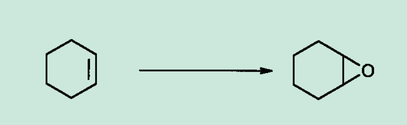
$$\mathrm{RX + ROH \rightleftharpoons ROR + HX} \quad \text{reaction 1}$$

$$\mathrm{HX + ROH \rightleftharpoons RX + H_2O} \quad \text{reaction 2}$$

(X can be bromide or iodide, but bromide is the ideal candidate). The clever step is that, under the reaction conditions chosen, the HX reacts with a molecule of alcohol to regenerate the alkyl halide (reaction 2). Thus the catalytic cycle is established, and reaction 1 can take place again. This cycle continues until HX is lost from the system, or until a phase separation occurs, which limits the efficiency of the reaction considerably. However, selectivity is very high in all cases studied. Even 2-phenylethanol derived ethers and halides reacted cleanly, without the expected competing elimination to give styrenes. Cyclopropylmethanol also reacts cleanly, without acid-catalysed rearrangement, further indicating the applicability of the process. Chiral alcohols are racemised, suggesting that an $S_N1$ mechanism operates (at least for secondary alcohols).

# New epoxidation methods

Improved methodologies for the preparation of epoxides are the subject of much effort. Two contrasting pieces of work have recently been published in *Chemical Communications*. The first (1998, p 2211) by Corma *et al*., describes improvements to the mesoporous titanium silicate Ti-MCM-41. This is a large pore version of the industrially important TS-1 zeolite, and can be used to epoxidise larger alkenes than the zeolitic material. Corma and his co-workers describe two methods that improve the efficiency of epoxidation using *tert*-butyl hydroperoxide. One method is to silylate the surface of the material, leading to a very hydrophobic material; the second is to remove water from the reaction media. Both approaches are thought to work due to the more efficient separation of water from the catalyst, reducing the amount of diol formed. The diol is a catalyst poison, and suppressing its formation results in an increase in selectivity to epoxide from *ca*. 90% to almost 100% in the case of cyclohexene.

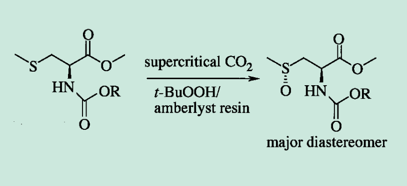


***Epoxidation of alkenes can be carried out using hydrophobic Ti-MCM-41 with t-BuOOH, or $(n\text{-}C_7F_{15})_2CO$ with $H_2O_2$.***

A second, quite different approach is that of Sheldon *et al. (Chem. Commun.* 1999, 263*)* who have used the fluorous biphase technology pioneered by Horvath in the mid-90s. (For a recent review see I. T. Horvath, *Acc. Chem. Res*., 1998, **31**, 641) This approach is centred round the remarkable ability of some heavily fluorinated compounds to be totally immiscible with organics at one temperature, but mix completely at a slightly higher temperature. Thus, many catalysts can be made with long perfluoro ‘pony tails’ such that they are soluble in fluorous phases. Raising the temperature slightly allows them to mix with an organic phase containing reactants and carry out catalysis. Following this the temperature is dropped and the fluorous phase, containing the catalyst is removed. Sheldon has applied this concept to the hexafluoroacetone / hydrogen peroxide system, a known epoxidising mixture. Whereas hexafluoroacetone is a very volatile compound, and requires extreme measures to efficiently condense it and keep it in the reactor, longer chain perfluoroketones do not suffer this drawback. Catalytic quantities of perfluoroheptadecanone were used with hydrogen peroxide to efficiently epoxidise a range of alkenes in high yield. The only co-product is water, making this process very environmentally acceptable.

# Remarkable pressure-dependent changes in diastereoselectivity in supercritical carbon dioxide

A further example of the remarkable utility of supercritical fluids was recently published by Christopher Rayner and his co-workers at Leeds University in the UK (*Chem Commun.*, 1999, 247). This time the supercritical medium was carbon dioxide. This is easily made supercritical, and there is a great deal of scope for variation in both temperature and pressure, both of which can change the properties of the fluid. Their latest article demonstrates the benefits of having the ability to tune the fluid to suit the reaction. The oxidation of chiral sulfides, such as those derived from the sulfur-containing amino acids cysteine and methionine, using *tert*-butyl hydroperoxide and an Amberlyst ion exchange resin leads to sulfoxides which are themselves chiral centres. Thus a pair of diastereomers is possible. In a remarkable piece of work, they have managed to show that variations in pressure during the reaction can change the diastereoselectivity from 0% up to a maximum of 95%. Such diastereoselectivity is possible in conventional solvent systems, but only with very careful choice of bulky substituents on the substrate, as opposed to the simple S-methyl and methyl ester substituents used in this work. Up to 50 bar pressure no d.e. was observed. Increasing the pressure further resulted in a steady increase up to 95% d.e. at pressures of just under 200 bar. Higher pressures led to a drop in d.e. to about 40%. The origin of these effects is still not known and is under investigation

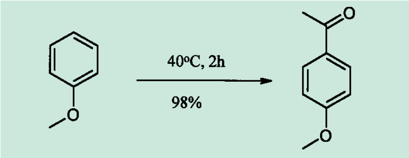


by the Leeds group. Whether these effects are general is not yet clear, but would have enormous implications for synthetic chemistry, where the achievement of high levels of control over diastereoselectivity is vitally important on many cases, but can often only be achieved with the use of complex directing groups, if at all. However, Rayner has indicated that other, as yet unpublished results indicate that the phenomenon may be quite widespread.

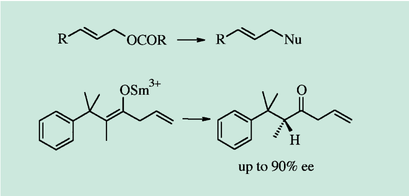
For more information on supercritical carbon dioxide see *Chem. Eng. News*, 15 February 1999, 12 and *Chem. Br.*, April 1999.

## Fluorous biphasic catalysis with metal-centred catalysts

This fluorous catalysis approach has been used by other workers recently in a variety of catalytic applications. Mikami *et al*. (*Synlett*, 1998, 1347) have developed a perfluoroalkyl sulfonamide complex of a lanthanide. This represents an interesting twist, as lanthanides are usually used as catalysts because of their ability to function as Lewis acids even in the presence of water. They have shown that the lanthanide species is capable of remarkably efficient catalysis using benzotrifluoride as solvent in a monophasic system. For example, anisole could be acylated in essentially quantitative yield in 2 hours at only 40 °C. This compares very favourably with conventional methods, which require significant quantities of catalyst, and generate a great deal of waste. Alcoholysis of anhydrides and Diels–Alder reactions are also discussed.



Other organometallic catalytic systems have also been investigated. Sinou *et al*. (*Tetrahedron Lett*., 1998, 9439) have used Pd complexes of polyfluorinated phosphines to carry out allylic alkylations in perfluorinated solvents/ THF biphasic mixtures. The mixtures became monophasic at around room temperature. Substitutions were typically complete in a few minutes, and the catalyst could be separated from products by cooling to 0 °C.



Curran and co-workers (*Tetrahedron Lett*., 1998, 8691) have effected catalytic enantioselective protonation of Sm enolates using fluorous proton sources. They achieved ee’s of up to 90%.

## Shift towards green practices in crop protection

In a press release from Frost and Sullivan the international marketing consultancy company (http://www.frost.com) the results from a new study on the European market for crop protection are summarised. Research and development has enabled better and more environmentally-friendly products to be launched onto the market and there will always be demand for crop protection. The shift towards green practices has led to the development of new, low-dose products with better pest-targeting capacities. New active ingredients which are less harmful to the environment and better able to target pests can earn high revenues for manufacturers, thus stimulating the market. Traditionally crop protection has proved an excellent method for minimising costs while maximising yields and some farmers have been reluctant to reduce the volume of crop protection used per hectare. However, this attitude is declining as concern for the environment heightens and farmers have the option of adopting integrated crop management as a positive step towards improving the environment. It is believed that farmer’s reliance on crop protection will, over time, decline.

## Vapour-free dissolution

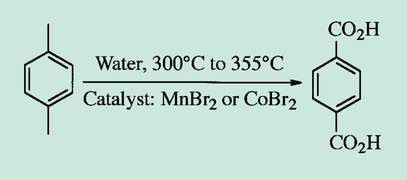
There is increasing pressure for the chemical industry to avoid volatile organic solvents, especially chlorinated compounds. The problem is to find alternatives. A little known area of chemistry, ionic liquids, could soon provide at least one way to carry out reactions without volatile solvents. Chemists at several centres around the world have found that they can turn a solid into liquid simply by tweaking their ions so that the crystalline form is less stable than the liquid. Important work, particularly relevant to petrochemicals, is being carried out at the French Petroleum Institute, France. The team have recently developed an ionic liquid system for converting feedstock alkenes using hydrogenation, isomerization and hydroformylation reactions. They also have a process available for licensing that uses ionic liquids to dissolve transition metal catalysts for converting butenes into iso-octenes, one of the raw materials for PVC plasticizers. The Queen's University of Belfast, UK, have another group leading the way to clean reactions. The team have raised more than £2 M (Euro 2.9 M) of support from industry and elsewhere. This funding, will help develop ionic liquids for clean syntheses of linear alkyl benzenes, the regioselective alkylations of aromatic amines and alcohols for epoxidations, the low-temperature reduction of aromatics to alicyclics and the oligomerization of butenes for making synthetic lubricants such as polyisobutene. [*The European Chemist* (January 1999) **1**, 22].

*Pesticides are now being applied in lower doses using improved application methods*

Photo: Graham Matthews, IPARC.

## Terephthalic acid production

The synthesis of terephthalic acid from *p*-xylene is one of the largest scale processes in the chemical industry. The hydrocarbon is currently oxidised using air in acetic acid as solvent, some of which is lost by 'burning' under the forcing conditions of the oxidation. The process is run at high temperatures and in the presence of metal bromides, leading to potentially severe corrosion problems. R. L. Holliday and his co-workers B. Y. M. Jong and J. W. Kolis (*J. Supercritical Fluids*, 1998, **12**, 255) have found that water at very high temperatures (close to supercritical and supercritical) is an excellent medium for the reaction.



They have successfully oxidised a range of alkyl aromatics with oxygen as the oxidant—the high temperature water being an excellent solvent for oxygen. They required a catalyst for reaction to occur—as in the traditional process, $MnBr_2$ and $CoBr_2$ were found to be the best, with other metal salts giving large quantities of char and coupling reactions.

## Converting the greenhouse gas carbon dioxide into acetone

Koji Tanaka and co-workers from the Institute for Molecular Science in Myodaiji, Japan, have developed a ruthenium naphthyridine complex that transforms carbon dioxide into acetone, an important feedstock for the chemical industry. In an electrolysis apparatus the Japanese team force the $CO_2$ to give away one carbon atom by transferring it to another carbon dioxide molecule, which is thus transformed into an electrically charged carbonic acid molecule. The remaining CO fragment is recompensed for its loss by the addition of a ruthenium compound to the reaction mixture. The compound takes the place of the lost oxygen atom and puts a pincer grip on the CO fragment. This doesn't last long however, because the hold is so loose that the pincer can be rapidly pushed aside by the carbon atom of an additional compound mixed into the reactor by the researchers. Once the pincer is completely forced away, the carbon dioxide is transformed to a molecule with three carbon atoms—acetone [*Angewandte Chemie, International Edition* 1999, **38**(3), 362-363].

## Biodiesel

The British Association for Bio Fuels and Oils (BABFO) believes that oilseed rape could supply 10% of the UK's diesel requirements for 2020 if the tax on its purchase was reduced to 10% of that on fossil-sourced diesel. The use of rape oil could be increased by blending it into fossil diesel at 5% as is done 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.

Bob Fox and Dan Ginosaur from Idaho National Engineering and Environmental Laboratory have discovered a chemical process to turn waste food-grade French fry oil into a higher quality biodiesel fuel faster, less expensively and with less waste than current processes. The new process uses a solid catalyst and eliminated the need for a base liquid, which also eliminates the need for acid to neutralise the base, and water to rinse away the acid—a problem of current processes. The process is continuous and produces food-quality glycerol as a byproduct. Sales of the glycerol to the food and beverage industry could pay for the entire process, bringing the price of the biodiesel down to the same price as regular petrodiesel.

## Glyphosate

1999 is the 25th anniversary of glyphosate—the enormously successful nonselective herbicide developed by Monsanto, but now off-patent in all countries except the USA, where is does not come off-patent until 2000. Traditionally the key intermediate disodium iminodiacetate (DSIDA) in glyphosate production has been synthesised by the Strecker process, which requires ammonia, formaldehyde, hydrochloric acid and hydrogen cyanide. The last of these chemicals is acutely toxic and requires special handling. Furthermore, since the process exothermically generates potentially unstable intermediates, special care must be taken to prevent runaway reactions. The overall process also generates up to 1 kilogram of waste for every 7 kilograms of product, and this waste must be treated prior to disposal.

The new Monsanto process for DSIDA production relies on the copper-catalyzed dehydrogenation of diethanolamine. The raw materials have low volatility and are less toxic. Process operation is inherently safer because the dehydrogenation reaction is endothermic and, therefore, does not present the danger of runaway reaction. In addition, this 'zero-waste' route to DSIDA produces a product which, after filtration of the catalyst, is of such quality that no purification or waste removal is necessary for subsequent use in the manufacture of glyphosate.

## Superabsorbent polymers for pesticide application

Helmut Brueggemann received the Huels Innovations Prize for 1998 for his application of superabsorbent polymers (used in hygiene products) to pesticide application. The pesticides are incorporated into the superabsorbent polymers, which are then fixed in the root area of the crops to achieve a controlled release of the substance over a long period of time. Pesticides will have to be applied only once a year with this new Culigel technology. Active substance requirements can be reduced by 90% and crop yield can be increased— *e.g.* by 20% in the case of potatoes. Further information can be obtained on http://www.huels.de.

## Read any green chemistry papers?

**If you have read any items relating from your literature reading which could be in the 'Perspectives' 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]**

# UK Government consultation paper

## on sustainable production and use of chemicals[1]

**Becky Allen reports on a paper which has been attacked by some sections of the chemical industry for not being radical enough**

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In its submission to the Department of the Environment, Transport and the Regions (DETR) the IChemE says: 'We are concerned that the focus [of the consultation paper] on extending current legislative regimes fails to encourage the radical approaches required to drive sustainability . . . Sustainability will only be achieved by a quantum change in approach by both industry and Government, and this message is sadly lacking.'

According to the IChemE: 'Very urgent action is needed by the chemical industry to set in motion profound structural changes which can only flow from a reexamination of the chemistry fundamentals which underpin it and the development of the process technologies to bring about the changes.'

These sentiments are echoed in the Royal Society of Chemistry's comments on the consultation paper. As well as needing 'step changes that go well beyond good housekeeping', the RSC says that the sustainable production and use of chemicals requires invention and development of new chemical science and technology.

> 'a step change is needed within academia and industry'
> (IChemE and RSC)

According to the RSC, this 'step change' will depend on a new approach by many academic and industrial chemists, as well as business managers: 'Sustainable performance can be a real commercial opportunity and worth the investment.' But Government money will be needed to fund the basic research, the RSC argues. 'Industry is unlikely to do this [basic research] on its own. Latest figures for the UK chemicals industry show a declining spend on all research and development as a percentage of sales,' the RSC points out.

> 'Government money will be needed to fund basic sustainable production research'

The Government's consultation paper says that a review of policy on chemicals in the environment is necessary because of factors like public attitudes towards chemicals, and the slow progress of risk assessing existing chemicals. In its response to Government, the Chemical Industries Association (CIA) says: 'A review is clearly needed. Despite industry's demonstrable improvements in performance, there has been a change in the degree of risk acceptable to society from chemicals in the environment and this must be addressed.'

Many consultees support the Government's suggestion of using a stakeholder forum to improve dialogue between industry and the public, although` some doubt the impact it can have. According to the CIA:'Transparency is essential in chemicals management [but] broadening public involvement will be difficult given the practical obstacles to genuine public dialogue.'

### Room for agreement?

As well as the IChemE, CIA and RSC, over 100 other organisations and individuals responded to the consultation paper, that posed several questions about the legal and policy framework (see box). The comments will form the basis of a White Paper due for publication in April. Comments came mainly from the chemical industry—including companies, trade associations and professional societies, but a significant number of environmental and health groups also responded. As a result there are divergent views among consultees on how to effect change, although most agree that change is necessary.

Differences of opinion are pronounced on several issues, including risk assessment, voluntarism and substitution. 'There are large differences between consultees' views on the proper scope of the review, effective methods for speeding up assessments, the correct rationale for controlling chemicals, and information exchange with the public,' says the DETR.

Most environmental groups that responded to the consultation paper are signatories to the Friends of the Earth (FoE) *Joint statement on chemicals and health*. The statement calls for a phase-

### Key questions

- **How effective is current legislation, and is framework legislation on chemicals needed at European or international level?**
- **How might an eco-efficiency programme be advanced in the chemical industry?**
- **How can the risk assessment process be accelerated?**
- **How can the decision-making process be made more transparent?**

out of persistent or bioaccumulative chemicals, and a move towards a positive licensing system for chemicals, placing the onus to prove that a chemical is safe on industry. Consultees from the chemical industry reject such proposals. ‘We are specifically opposed to a regulatory approach based on the ‘reverse burden of proof’, comparative assessment and hazard substitution,’ says the CIA.

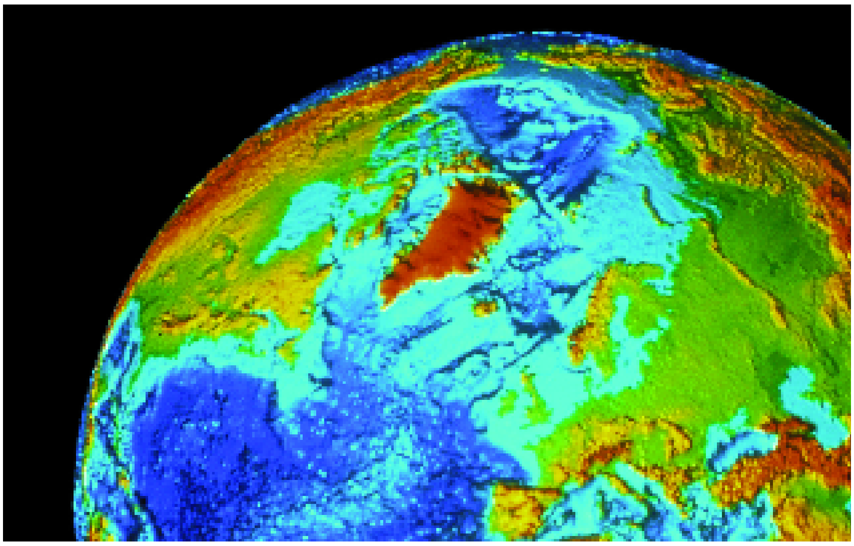
## Risk assessment, substitution and the carrot or the stick?

Despite widespread agreement among consultees that risk assessment under the Existing Substances Regulation must be speeded up, there is no consensus about how to achieve this. Environmental groups also regard the risk assessment process as deeply flawed. But many consultees from industry agree that new schemes are not the way forward. ‘We have severe doubts about a duplicative scheme being created in the UK and firmly believe that no new national schemes should be started for the testing and assessment of chemicals. Global resources for chemicals management are already scarce and those that do exist must be focused on the key issues,’ says CIA.

‘change must be based on the voluntary principle’
(CIA)

‘regulatory action is essential’
(Friends of the Earth)

Although most responses from the chemical industry stress that any change must be based on voluntary principles, environmental groups say that the stick must accompany the carrot. According to FoE: ‘The crucial role of Government [is] in transforming industry and stimulating innovation, through technology-forcing regulation, rather than voluntary agreements, which tend to reduce innovation . . . Friends of the Earth does not consider that a voluntary approach is adequate either to protect human health or to promote innovation. Regulatory action is essential.’



*Environmental organisations favour a positive licensing system for chemicals*

Greenpeace also thinks that innovation can be stimulated by a greater emphasis on substitution. The group’s submission argues that substitution will create new markets for the replacement of hazardous chemicals by less hazardous alternatives. According to Greenpeace: ‘Substitution of hazardous chemicals is one feature of a new policy that has real potential to move the chemicals sector onto a more sustainable path.’

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[1] Sustainable Production and Use of Chemicals: Consultation Paper on Chemicals in the Environment. Department of the Environment, Transport and the Regions (1998). (http://www.environment.detr.gov.uk/sustainable/chemicals/consult/index.htm).

## ITALY

# Green chemistry in Italy

### Italian green chemistry recognition program

On February 22nd, Italy's National Interuniversity Consortium of Chemistry for the Environment (INCA) launched a annual recognition program of industrial contributions in ‘Green Chemistry’ / ‘Clean Chemical Production Processes.’ The formal recognition program was part of the annual INCA meeting in Venice, Italy where representatives of some 30 Italian universities gathered to discuss their programs in chemistry for the environment and to map out research and education strategies for the Consortium over the next 5 years. INCA recognized three companies this year. The first award went to Lonza Intermediates and Additives, S.A. for its ‘Process Optimization of the Oxidation of *o*-Xylene to Phthalic Anhydride by the Selective Transformation of Reaction Intermediates.’ The second company honored was Mapei, S.p.A. for its development of ‘Very Low VOC Emitting Adhesives, ‘and the third, Solvay, Italia for its process ‘Recovery of Residues from Fume Purification Plants and their Reutilization as Feedstocks.’

Each of the 1999 INCA recipients received a dish engraved citing their specific contribution. Participants in the recognition program included representatives from the Italian Ministry for Industry, the Italian Institute for Health, the Venetian Regional Program for the Modernization of Industry in Porto Marghera, and the U. S. Environmental Protection Agency's Green Chemistry Program. The INCA recognition program is the first OECD country to formally implement an awards program as one of the recommendations contained in the OECD Working Party for Sustainable Chemistry report of October 1998. The OECD recommendation for member countries to implement industrial recognition programs was based on the highly successful Presidential Green Chemistry Challenge Awards program now in its fourth year in the United States.

For further information contact: Professor Pietro Tundo, University of Venice: tundop@unive.it or the INCA website: hydra.unive.it/inca out of persistent or bioaccumulative chemicals, and a move towards a positive licensing system for chemicals, placing the onus to prove that a chemical is safe on industry. Consultees from the chemical industry reject such proposals. 'We are specifically opposed to a regulatory approach based on the 'reverse burden of proof', comparative assessment and hazard substitution,' says the CIA.

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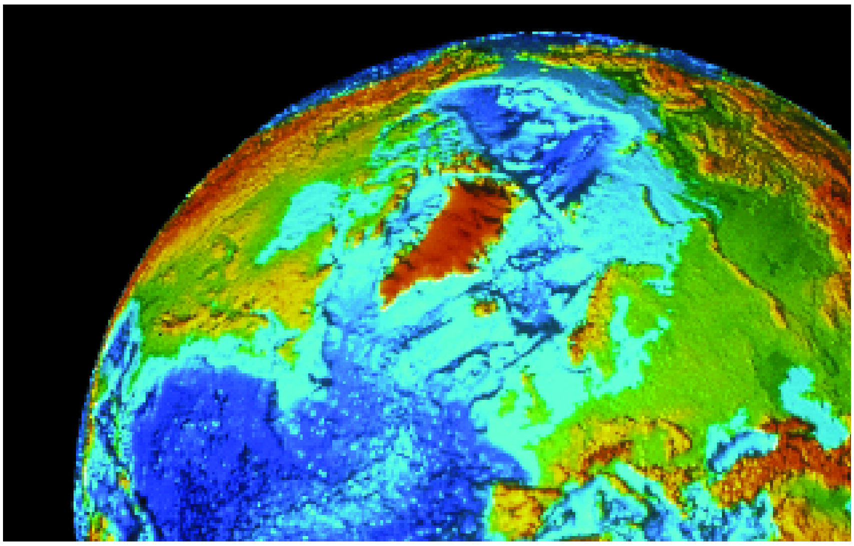

*Environmental organisations favour a positive licensing system for chemicals*

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# Cleaner synthesis seminar

On 19 January this year a half-day meeting was held at Lancaster University's conference centre on the topic of 'Cleaner Synthesis'. I hope I need not write of the importance of this area to readers of this journal, since green chemistry is of course primarily concerned with minimizing the impact our activities have upon our ever more fragile environment. Clean synthesis is of course a multifaceted area that covers chemical aspects such as strategies for the synthesis of chemicals and immobilization strategies through to engineering-based approaches, such as new technologies for reactor design, monitoring of effluent and energy usage, *etc*. We decided, however, in this meeting to focus on the chemical/materials aspects of the subject with a view to providing a tight focus for the afternoon. At this point I should mention the input of Lancaster Synthesis, whose generous sponsorship made the meeting possible.

Owing to our tight schedule we began proceedings rather earlier than usual and kicked off with an enthusiastic talk from Steve Howdle of Nottingham University. Steve told us how his group are using supercritical fluids such as carbon dioxide in polymer synthesis and processing. An unusual aspect of the work appears to be the effect of stirring on the progress of these radically initiated polymerization reactions. Steve discussed the observed poor performance of reactions carried out with efficient stirring in terms of interactions of the reactor vessel wall with the polymerization system. We also heard how polymers processed with supercritical fluids are being used to imbibe drugs and possibly even produce new artificial bone materials. Next to speak was Ron Grigg of Leeds who discussed some new cascade cycloaddition reactions based mainly on 1,3-dipolar additions with nitrones. As well as producing some exciting new synthetic chemistry we heard how cascade-type processes can provide cleaner synthetic alternatives to traditional stepwise synthesis by reducing the number of work-up steps required both in the laboratory and on a larger scale. Continuing with this theme of waste minimization and ease of work-up our next speaker, James Clark from York, discussed a large range of silica-immobilized catalysts that are finding uses in an ever more numerous areas of chemical manufacture. New catalysts included solid bases and acids and new oxidants. The alternative support materials to inorganics such as the silicas are synthetic polymers. Work began in this area back in the 1970s but oddly it's only recently that the chemical community has begun to appreciate the advantages of polymer-supported strategies. Our next speaker, David Sherrington, has been at the forefront of research in this area continuously from the initial 1970s burst of interest through

to the current renaissance in the field. His talk centred on polyimide support materials and included descriptions of how the nature of the polymer support can effect the course of the reaction. The advantage of polyimides over the conventional polystyrenes is of course superior thermal stability. Our final speaker David Gani broadened the scope of the meeting by describing how the design of drug molecules can be achieved by careful examination of active sites in the relevant enzymes. He also described his groups preliminary work on using functionalized polytetrafluoroethylene another candidate for a support that has good chemical and thermal stability. Clearly supports based on this stable and tough polymer could in the future revolutionise supported synthesis.

Thus we brought the proceedings to a close and retired to our apres-seminar discussion groups, lubricated by generous sponsorship from Lancaster Synthesis, in Cartmel College's bar! Overall the event was well attended with a good number of people who had travelled some distance. Those of you who missed the event can all look forward to the sequel in due course.

*Steve Rimmer, The Polymer Centre, Lancaster University*

## Yale Corporate Environmental Leadership Seminar

Yale University are running a Corporate Environmental Leadership Seminar in New Haven, Connecticut between June 6 and June 17, 1999. The course is intended to offer state-of-the-debate assessments of contemporary issues, to sharpen tools needed for environmental management and to enhance the strategic thinking of participants. The course is delivered by a distinguished group of faculty members from Yale's Law, Medical, Management and Forestry and Environmental Studies Schools as well as outside experts through a mix of discussions, problem-solving exercises, and case studies. A mix of professionals from various industries as well as government and non-governmental organisations are invited to enhance discussion and interaction across sectors. The 1999 Seminar will place emphasis on international issues, public and private roles, practical implications of industrial ecology and leadership activities.

Photo: Michael Marsland, Yale University, Office of Public Affairs.

*Further information can be obtained from Janet Testa or Marion Chertow at the Yale School of Forestry and Environmental Studies, 205 Prospect Street, New Haven, Connecticut 06511-2189, USA , email:janet.testa@yale.edu or via the web site: www.yale.edu/cels.*

## Green 'swap shop'

The University of Sheffield's Environmental Business Network, in conjunction with the RSC Green Chemistry Network and Yorkshire and Humberside Chemicals Sector, are organizing a 'Swap Shop' on the theme of 'Waste Minimization and Measurement'. The Swap Shop will be held on 17 May at the Tankersley Manor Hotel in Barnsley, UK. The morning session will include several presentations on relevant legislation together with examples from industry on Best Practice. The afternoon will take the form of poster session with participants able to display information on 'Technology Offered and Wanted' There will also be a series of surgeries in the afternoon where participants will be able to 'drop in' and discuss issues with relevant experts.

For more information contact Angela Bottom on (0114) 222 4600 E.mail:EBN@sheffield.ac.uk or greennet@york.ac.uk

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## Arranging or attending any green chemistry events?

**If you have any items about conferences, seminars etc. which could be included in the events or conference diary sections 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]**

# Conference Diary

## JUNE 1999

**HELECO ‘99 Environmental Technology for the 21st Century: 3rd International Exhibition and Conference** **June 3–6**
Thessaloniki, Greece
(erasmhor@athena.compulink.gr)

**Oilseed Rape Pipeline** **June 8**
UMIST, Manchester, UK
(http://www.actin.co.uk)

**NATO Advanced Study Institute- Enzymes in Heteroatom Chemistry: Green Solutions for Chemical Problems** **June 19–30**
Best Western Hotel ERICA, Berg en Dal, Netherlands
(http://www.sci.kun.nl/orgchem/general/agenda/nato-kun.html)

**5th International Interdisciplinary Conference on the Environment** **June 23–26**
Baltimore, Maryland, USA
(http://champion.iupui.edu/~mreiter/iea.htm)

**Schools Summer Lecture: To Planet Earth with Love from Chemistry** **June 24**
Sheffield University, UK
(http://www.rsc.org/lap/rsccom/locsecs/localsec57.htm)

**3rd Annual Green Chemistry and Engineering Conference: Moving Towards Industrial Ecology** **June 29–July 1**
National Academy of Sciences, Washington D.C., USA
(http://www.acs.org/meetings/greencfp.htm)

## JULY 1999

**Gordon Research Conference on Green Chemistry** **July 10**
Queen’s College, Oxford, UK
(jhc1@york.ac.uk)

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

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

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

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

**SAC ‘99 (Analytical chemistry)** **July 25–30**
Dublin City University, Ireland
(http://www.dcu.ie/chemistry/sac99/sac99.html)

## AUGUST 1999

**218th American Chemical Society National Meeting, with half-day symposium on Green Chemistry** **August 22**
New Orleans, USA
(natlmtgs@acs.org)

## SEPTEMBER 1999

**Electrochem ‘99** **September 1–3**
University of Portsmouth, UK
(http://sci.mond.org/conference/home.html)

**4th European Congress on Catalysis (Europacat 4): Catalysis and Chemical Technologies for a Sustainable Future** **September 4**
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)

**Euromembrane ‘99** **September 19**
Belgium
(http://www.vito.be/euromembrane99/)

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

## OCTOBER 1999

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

**2nd Pan Pacific Conference on Pesticide Science** **October 24–27**
Waikiki, Honolulu, Hawaii
(http://www.acs.org/meetings/ppc/welcome.htm)

# Toward a 'reagent-free' synthesis

## Tandem enzymatic and electrochemical methods for increased effective mass yield (EMY)†

**Tomas Hudlicky,* Dean A. Frey, Lukasz Koroniak,‡ Christopher D. Claeboe and Larry E. Brammer Jr.**

*Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA*

*Received 19th February 1999*

## Summary

Several synthetic pathways to cyclohex-5-ene-1*R*,2*S*,3*R*,4*R*-tetrol (conduritol C) and cyclohex-5-ene-1*S*,2*R*,3*R*,4*R*-tetrol (conduritol F) are compared; each is analyzed for effectiveness of waste minimization. The latest synthesis, reported in this manuscript, combines enzymatic transformations with electrochemical methods. The concept of "effective mass yield" (EMY) is defined and illustrated.

## Introduction

The definition of efficiency with respect to organic synthesis varies according to the source or the focus of a pertinent activity. For example, academic researchers define efficiency (of a total synthesis) in terms of overall chemical yield and/or brevity of design.[1] A process chemist, on the other hand must also be concerned with generation of bulk waste (organic and inorganic) and the ratio of such weight to that of the desired product. Finally, the economics of cost and energy expenditures all enter into consideration for compounds about to enter the market place. Of the various definitions, Wender's covers most of these issues: '*the ideal synthesis . . . may be defined as one in which the target molecule is prepared from readily available starting materials in one simple, safe, environmentally-acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.*'[2] Sheldon defines the efficiency and environmentally benign nature of a synthesis in terms of an environmental factor or *E*-factor: the ratio of the mass of byproducts to the mass of the product.[3] At the same time he considers the stoichiometry of the reaction (*i.e.* catalysis) as a contributing factor to the overall efficiency.[4] The concept of 'atom economy' has been advanced by Trost,[5] and it has also been addressed by Sheldon in a recent review.[6]

In this manuscript we compare several approaches to conduritols and provide 'effective mass yield,' which we define as the percentage of the mass of desired product relative to the mass of all non-benign materials used in its synthesis. It can be approximated as 1/*E* where *E* is as defined by Sheldon,[3] with one additional consideration: those byproducts, reagents or solvents that have no known environmental risk associated with them (for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, *etc.*) do not enter into the calculations. A qualitative attempt at such a classification was made by Sheldon (environmental quotient or EQ).[3] By looking at the percentages of effective mass yield (EMY) for several synthetic pathways, one sees that neither atom economy, brevity nor chemical yields by themselves provide an accurate picture of the overall processes with respect to the total waste component.

## Results and discussion

Several conduritol syntheses (Schemes 1–3) are analyzed for effective mass yield: Weinreb's classical synthesis,[7] a preparation that utilizes an enzymatic step,[8,9] and one in which electrochemistry has been employed.[10] These three preparations are compared for relative efficiency in terms of overall chemical yield (as reported), Sheldon's *E* value, and the effective mass yield (EMY). The weights of autoclaved cell masses, water, ethanol, methanol, and acetic acid are not taken into account because of their nontoxicity in the environment.[11] The EMY values are therefore calculated without the masses of these solvents. It follows that nonhazardous solvents should be used in all synthetic ventures to maximize EMY values.

### Green Context

**This paper describes a new synthetic route to conduritols C and F, based on a combination of enzymatic dihydroxylation and electrochemical reduction. In comparing this new approach to earlier syntheses, the author proposes a new measure of 'environmental friendliness'—effective mass yield, defined as the 'mass of desired product compared to the mass of all non-benign materials used in its synthesis'. This approach augments and complements Sheldon's *E*-factor and environmental quotient. *DJM***

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† Supplementary data available: effective mass yield calculations. For direct electronic access see http://www.rsc.org/suppdata/gc/1999/57/, otherwise available from the British Library (BLDSC, No. SUP 57506, 2 pp.) or the RSC Library. See Author Guidelines (inside back cover, or http://www.rsc.org/greenchem).

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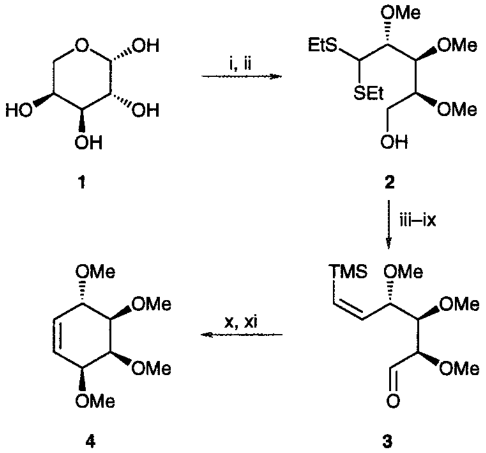
In the classical synthesis, Scheme 1, standard synthetic operations are used to convert arabinose to the final product.[7] It should be noted, however, that the tetramethyl derivative of conduritol C (**4**) requires deprotection ($BBr_3/CH_2Cl_2$), with uncertain outcome, as the transformation was not performed by the authors. Even a successful deprotection would reduce the calculated yield. Scheme 1 shows the mass ratios for this preparation.

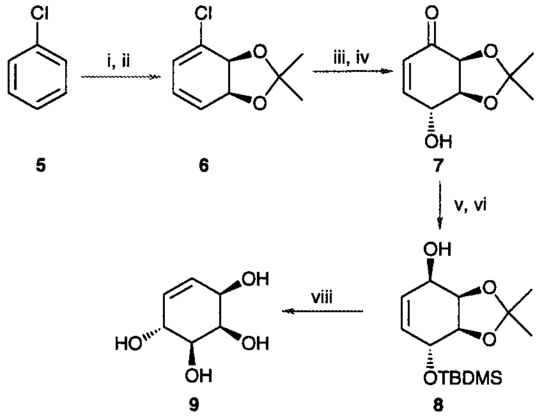


**Scheme 1.** Overall yield = 8.8%; *E* = 625; EMY = 0.16%. *Reagents and conditions*: i, $(CH_3O)_2SO_2$, NaOH, $H_2O$; ii, EtSH, HCl; iii, *tert*-butyldimethylsilyl chloride, imidazole, 4-dimethylaminopyridine, dimethoxyethane; iv, $HgCl_2$, HgO, acetone–$H_2O$; v, $PPh_3$, $CBr_4$, $CH_2Cl_2$, $Et_3N$; vi, *n*-BuLi, TMEDA, THF, TMSCl; vii, Pd($BaSO_4$), pyridine; viii, HOAc–$H_2O$ (2:1); ix, dimethyl sulfoxide, $(COCl)_2$, $CH_2Cl_2$, $Et_3N$; x, $SnCl_4$, $CH_2Cl_2$; xi, AgO, MeI.

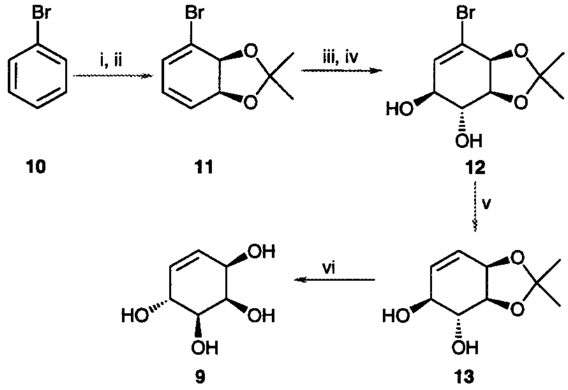
The syntheses of conduritols F[8] and C[9] from arene *cis*-dihydrodiols obtained by enzymatic oxidation of halobenzenes with *E. coli* JM109 (pDTG601) have been accomplished in our laboratories.[12] In an effort to incorporate environmentally benign protocols that utilize less reagent and solvent mass to achieve the syntheses, we have investigated alternative methods for the epoxidation of C4–C5 olefin and for the reduction of vinyl halides at C1. For example, in our earlier synthesis of conduritol F,[8] the oxidative functionalization at C4–C5 (*m*-chloroperbenzoic acid; methylene chloride) was followed by reduction of the vinyl halide (tri-*n*-butyltin hydride, AIBN), to the protected conduritol F. Similar chemistry was also used to attain conduritol C (**9**), as shown in Scheme 2.

In the ‘green’ synthesis of conduritol F, the epoxidation with *m*-chloroperbenzoic acid in methylene chloride has been replaced with either bromohydrin generation or environmentally friendly carbodiimide-promoted olefin epoxidation with aqueous hydrogen peroxide to form the *anti*-epoxide, as reported by Majetich *et al.*[13] The tri-*n*-butyltin hydride reduction of vinyl halide **12** was replaced with an electrochemical reduction, which we have developed in our laboratory,[10] to give a 60% yield of the protected conduritol F.

Although our conventional synthesis of conduritol C[9] (Scheme 2) is the shortest on record, it still contains a number of environmentally “unfriendly” chemical transformations. The EMY value for this synthesis is comparable to that of the completely chemical preparation. When the enzymatic step in the latest preparation (Scheme 3) was augmented with electrochemical reduction rather than traditional tri-*n*-butyltin hydride-mediated dehalogenation, the component of byproduct mass was further reduced, indicated in an increased EMY value.



**Scheme 2.** Overall yield = 26.9%; *E* = 1125; EMY = 0.12%. *Reagents and conditions:* i, *E. coli* JM109 (pDTG601A); ii, 2,2-dimethoxypropane, acetone, *p*-TsOH; iii, $O_2$, tetraphenylporphine, $CCl_4$, *hν*; iv, thiourea, MeOH; v, *tert*-butyldimethylsilyl chloride, dimethyl formamide; vi, L-Selectride, THF; vii, HCl, $H_2O$.



**Scheme 3.** Overall yield = 23.9%; *E* = 391; EMY = 2.39%. *Reagents and conditions:* i, *E. coli* JM109 (pDTG601A); ii, 2,2-dimethoxypropane, acetone, *p*-TsOH; iii, 1,3-dibromo-5,5-dimethylhydantoin, $H_2O$–acetone; iv, NaOH, $H_2O$–dimethoxyethane, heat; v, $e^-$, MeCN, $Et_4NBr$; vi, NaOBz, $H_2O$.

In order to determine the overall efficiency of the syntheses, effective mass yields were calculated[14] for conventional and ‘green’ syntheses of conduritol C, as shown in Schemes 1 and 2. Effective mass yield accounts for not only atom economy,[5] (*i.e.*, ‘how much of the reagent mass ends up in the product’), but also those materials such as solvents and reagents that do not contribute to the mass of accumulated byproducts. Hence effective mass yield is a more accurate representation of (desired) mass expressed as a percent of the total mass of materials used in manufacturing.

## Acknowledgements

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## References

1 T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3.

2 P. A. Wender and B. L. Miller, *Organic Synthesis: Theory and Applications*, ed. T. Hudlicky, JAI Press, Greenwich, CT, 1993, vol. 2, pp. 27–66.

3 R. A. Sheldon, *Chemtech*, 1994, 38.

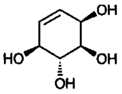
4 R. A. Sheldon, *Chem. Ind.*, 1997, 12.

5 B. M. Trost, *Science*, 1991, **254**, 1470.

6 R. A. Sheldon, *Chem. Ind.*, 1992, 903.

7 S. M. Weinreb and M. C. McIntosh, *J. Org. Chem.*, 1993, **58**, 4823.

8 T. Hudlicky, H. Luna and H. F. Olivo, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2907.



conduritol F

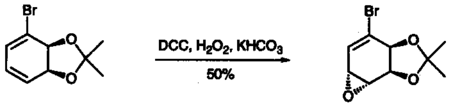
9 T. Hudlicky, R. Fan, T. Tsunoda and H. Luna, *Isr. J. Chem.*, 1991, **31**, 229.

10 T. Hudlicky, C. D. Claeboe, L. E. Brammer Jr., L. Koroniak and I. Ghiviriga, *J. Org. Chem.*, 1999, submitted.

11 For toxicity and pollution limits for these solvents see: (*a*) K. Verschueren, *Handbook of Environmental Data on Organic Chemicals*, Van Nostrand Reinhold, New York, 1983; (*b*) P. H. Howard, *Handbook of Enviromental Fate and Exposure Data for Organic Chemicals*, Lewis Publishers, Chelsea, MI, 1990.

12 For comprehensive reviews of arene *cis*-diol chemistry see: (*a*) S. M. Brown and T. Hudlicky, *Organic Synthesis: Theory and Applications*, ed. T. Hudlicky, JAI Press, Greenwich, CT, 1993, vol. *2*, pp. 113–176; (*b*) D. A. Widdowson, D. W. Ribbons and S. D. Thomas, *Janssen Chim. Acta*, 1990, **8**, 3; (*c*) H. A. J. Carless, *Tetrahedron: Asymmetry*., 1992, **3**, 795; (*d*) T. Hudlicky and J. W. Reed, *Advances in Asymmetric Synthesis*, ed. A. Hassner, JAI Press, Greenwich, CT, 1995, pp. 271–312; (*e*) T. Hudlicky, *Green Chemistry: Designing Chemistry for the Environment*, ACS Symp. Ser. 626, ed. P. T. Anastas and T. C. Williamson, American Chemical Society, Washington, DC, 1996, ch. 14; (*f*) T. Hudlicky and A. J. Thorpe, *Chem Commun*., 1996, 1993; (*g*) T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3; (*h*) T. Hudlicky, D. A. Entwistle, K. K. Pitzer and A. J. Thorpe, *Chem. Rev.*,1996, **96**, 1195; (*i*) A. D. Grund, *SIM News*, 1995, **45**, 59; (*j*) D. R. Boyd, *Nat. Prod. Rep.*, 1998, 309; (*k*) T. Hudlicky, D. Gonzalez and D. T. Gibson, *Aldrichim. Acta*, 1999, in press.

13 (*a*) G. Majetich, R. Hicks, G. Sun and P. McGill, *J. Org. Chem.*, 1998, **63**, 2564; (*b*) G. Majetich and R. Hicks, *Synlett*, 1996, 649.



14 All calculations are shown in tabular form in the Supplementary Material, (see footnote †).

*Paper 9/01397K*

# Thermal fixation of sulfur dioxide

## as elemental sulfur or sulfate with sodium oxalate

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*Received 14th January 1999*

## Summary

In a new thermal reaction, gaseous $SO_2$ is reduced to elemental $S_8$ over powdered $Na_2C_2O_4$ at 370 °C. Mixtures of $SO_2$ and dry air gave oxidation to sodium sulfate.

## Introduction

Sulfur dioxide is a troublesome pollutant arising from volcanic activity but also formed in many combustion processes. Human activities account for the release of as much as $2 \times 10^8$ tonnes $y^{-1}$. This release contributes to acid precipitation and the consequent degradation of forest. $SO_2$ decomposes thermally at very high temperatures, photochemically by irradiation with UV light, radiochemically by γ-rays, in electrical discharges and electrolytically.[1] In these reactions, $SO_2$ is believed to react *via* reduction to $SO_2^{\cdot -}$ and then SO. Since SO (detected spectroscopically) rapidly disproportionates to $S_8$ and $SO_2$, the observed products are $S_8$, $O_2$ and $SO_3$.[1]

Large quantities of sulfur dioxide, emitted into the atmosphere by the combustion of fossil fuels and the smelting of sulfide ores,[2] become oxidized to sulfuric acid and contribute to acid rain. The average lifetime of sulfur dioxide in the atmosphere has been estimated to be in the range of 3–10 h.[3a,b] Measurements of the acidity of snow and rain have shown that in parts of the eastern US and western Europe precipitation has changed from a nearly neutral pH 200 years ago to pH 4–5 today;[3a] in extreme cases, (Scotland, 1974) the rain had a pH of 2.4, equivalent to the acidity of vinegar.[3a] Taller stacks have been constructed to relieve local pollution problems.[3a] However, this has turned local problems into regional ones.

Removal of $SO_2$ from gas streams is possible by absorption of this acid gas by bases such as NaOH,[4c] but the resulting sulfites are not innocuous because disposal is needed and inadvertent acid treatment releases the $SO_2$ once again. Air oxidation of aqueous solutions of sulfites is possible and it has been extensively studied, but this adds a second step and the need for an external oxidant, a solvent and a catalyst.[4d] Methods for the recovery and removal of $SO_2$ from effluent gases involve reduction to elemental sulfur.[5]

Allied Signal[5] commercialized a method for converting $SO_2$ into $S_8$ in 1970 as an emission control system for a Canadian sulfide ore roasting facility. It can be applied for gas streams containing 4–100% $SO_2$, and for concentrations below 4%, a preliminary concentrating process is combined. Although the whole process is complex and involves eleven different elements and compounds, the main reductant is methane. Other reduction precesses for the reduction of $SO_2$ to $S_8$ involves the use of $H_2S$ (Claus process) or CO (Bureau of Mines) as reducing agents.[5]

The oxidation of $SO_2$ to $SO_3$ is, by far, the most important reaction in the chemistry of the oxides of sulfur.[2] In the presence of Pt, the reaction begins at 200 °C.[6a] In practical operations, the reaction is carried out at 450 °C using Pt or $V_2O_5$ as catalyst. $V_2O_5$ is preferred as catalyst because it is cheaper than Pt and less susceptible to poisoning by selenium and arsenic.[7] A scheme has also been proposed[8] for the oxidation of $SO_2$ to $SO_3$, with $V_2O_5$ on silica as catalyst.

In this paper we describe a new and convenient thermal method for the reduction of $SO_2$ to elemental $S_8$. When the reaction is used for the removal of $SO_2$ from air mixtures, oxidation of $SO_2$ to $Na_2SO_4$ takes place instead.

## Results

We previously reported that powdered sodium oxalate at 450–460 °C is an efficient selective reducing agent for highly unreactive species such as fluorocarbons, converting perfluorodecalin to perfluoronaphthalene, for example.[9] The ready availability of the reagent ($8/kg in bulk) permits the method to be considered for commercial application. We therefore examined it for the reduction of $SO_2$.

Passing $SO_2$ over a packed bed of powdered $Na_2C_2O_4$ at 370 °C led to the production of elemental sulfur by reduction of $SO_2$. Not all the $SO_2$ was destroyed in this one-pass apparatus, but in a multipass apparatus with trap-to-trap distillation using dry ice cooling of the sink trap, three passes were found to be sufficient to reduce the whole charge of $SO_2$ (5.23 g, 81.7 mmol, 95%) according to the following equation.

$$2Na_2C_2O_4 + 3SO_2 = 2Na_2SO_3 + 1/8S_8 + 4CO_2 \quad (1)$$

The expected amount of sulfur was removed from the oxalate bed by extraction with $CS_2$ to constant weight. The unreacted $Na_2C_2O_4$ was determined by titration with $KMnO_4$ solution and the $Na_2SO_3$ product by titration with $NaI_3$ solution. In the titration of $Na_2SO_3$ with $I_2$, $Na_2SO_3$ is oxidized to $Na_2SO_4$ and we also

### Green Context

**The conversion of sulfur dioxide from a pollutant into a useful raw material such as elemental sulfur or sulfate is a valuable achievement. This paper describes such conversions using reactants such as sodium oxalate. This is a new reaction—under non-aerobic conditions the product is sulfur, under oxidative conditions, sulfate is formed.** ***DJM***

determined the amount of $Na_2SO_4$ formed by precipitation with $BaCl_2$ and gravimetric determination of the resulting $BaSO_4$. We found that the moles of $Na_2SO_3$ determined by titration and the $Na_2SO_4$ determined gravimetrically were identical, indicating that no $Na_2SO_4$ was formed when $SO_2$ was passed through the oxalate bed. After the $SO_2$ was consumed, the $CO_2$ formed gave an acid soluble precipitate ($CaCO_3$) from $Ca(OH)_2$(aq) but was not determined quantitatively.

To examine potential applications for removing $SO_2$ from air, we moved to mixtures of $SO_2$ and dry air and found that neither sulfite nor sulfur were now formed. Since these two species were found to be stable to air at the temperatures of the reaction, they are not being formed and then subsequently oxidized by air. Therefore, a different pathway must be involved.

A 1:1 (v/v) $SO_2$/dry air mixture was passed over powdered sodium oxalate in a single-pass reactor. The stoichiometry of eqn. (2) was determined for this new reaction as follows. The sulfate was determined gravimetrically with $BaCl_2$. Sodium sulfite was absent because the bed residue showed no reaction with aq. $NaI_3$. Finally, one mole of oxalate, determined by titration with $KMnO_4$ of the oxalate remaining, was found to be consumed per mole of sulfate formed.

$$Na_2C_2O_4 + SO_2 + O_2 = Na_2SO_4 + 2CO_2 \qquad (2)$$

We have applied this reaction to the removal of $SO_2$ from air mixtures using single pass and multiple pass apparatus. In the single pass apparatus, where excess air is present, we found that as the length of $Na_2C_2O_4$ bed increases, so does the %$SO_2$ removed (Fig. 1). The percentage of $SO_2$ removed was determined by measuring the different amounts of $SO_2$ absorbed in a solution of $NaI_3$ when identical gas flow was passed through a cold and a hot oxalate bed.

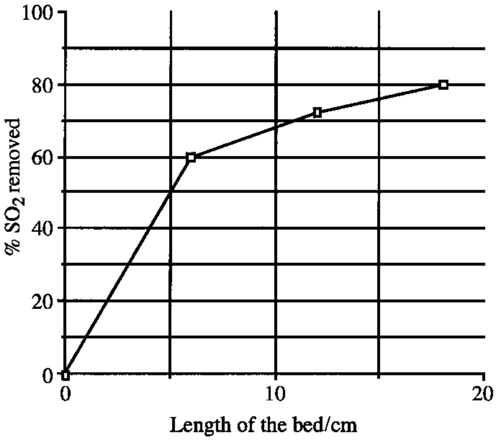

**Fig. 1** Efficiency of $SO_2$ removal *versus* bed length.

We have also used the trap to trap multipass apparatus in the presence of dry air by passing a 1:1 (v/v) $SO_2$/air mixture through the bed and condensing the unreacted $SO_2$. The condensed $SO_2$ was passed back and forth from trap to trap in a stream of excess dry air until the reaction finished. By connecting the exit of the apparatus to a 0.05 M $NaI_3$ solution, we were able to determine the amount of $SO_2$ that escapes the apparatus because of imperfect cooling of the trap. We found that 89% of $SO_2$ was retained in the bed as $Na_2SO_4$ and *ca.* 10% escapes. There is no significant $SO_2$ absorption in the cold bed.

Other substrates were not reduced under these conditions. For example, $(C_6H_5)_3PO$, $(C_6H_5O)_3PO$, $(CH_3)_2SO_2$ and $(CH_3)_2SO$ were unchanged when passed through the sodium oxalate bed at temperatures of 370 °C to 450 °C.

## Mechanism

The main point of this paper is to report the results, but some preliminary mechanistic discussion is presented here.

### Sulfur formation

A number of possible mechanisms might operate for the reduction of $SO_2$ to $S_8$. The most plausible intermediates seem to be $SO_2^{\cdot-}$ and then SO, as previously proposed.[1] The known disproportionation of SO to give $S_8$ and $SO_2$, followed by absorption of the acidic $SO_2$ by the basic $Na_2CO_3$ formed on oxidation of oxalate, is expected to yield the other observed product $Na_2SO_3$.

### Sulfate formation

The $SO_2$ oxidation with air raised the question whether $SO_2$ or $O_2$ or even $CO_2$ (300 ppm in air) was reacting with oxalate. Passing pure dry air over the oxalate bed at the reaction temperature produced no change in the bed instead of the oxidation of the oxalate to $Na_2CO_3$ that we had originally expected, so neither $CO_2$ nor $O_2$ react directly. Other work[9b] shows that even pure $CO_2$ does not react with hot sodium oxalate. It might seem remarkable that a reagent that reduces such inert substrates as perfluorocarbons and even CFCs[10] fails to react with $O_2$, but an important caveat is that the temperature used here (370 °C) is far lower than in the fluorocarbon work (465 °C) and mechanistic work on the fluorocarbon reaction shows that incipient decomposition of the oxalate to carbon is required for reaction with the fluorocarbons. Given that $O_2$ does not react with the oxalate, the most likely possibility is that $O_2$ intercepts a reduction product from the $SO_2$. The three most plausible candidates are the 1-, 2- and 4-electron reduction products of $SO_2$: $SO_2^{\cdot-}$, SO and S atoms.

Eqn. (3)–(7) illustrate a proposed mechanism *via* SO as intermediate. Sulfur monoxide, which can be formed when $SO_2$ is reduced with sulfur vapor in a glow discharge,[6b] has been considered as an intermediate in other reduction reactions of $SO_2$ to $S_8$.[6] Since it is unstable at all temperatures it disproportionates into $S_8$ and $SO_2$. However S atoms readily react with oxygen to give $SO_2$.[11] Another difficulty with this mechanism is that the oxygen atom removed from the $SO_2$ by sodium oxalate to generate SO, would be expected to initially appear in the product in the form of $Na_2CO_3$ as shown in eqn. (3). In the presence of $SO_2$ this carbonate would be converted to $Na_2SO_3$. For the observed product to be $Na_2SO_4$, the initially formed $Na_2SO_3$ would have to be oxidized by air. We find, however, that $Na_2SO_3$ is stable to dry air under our reaction conditions. Therefore a mechanism involving SO and S atoms as intermediates seems unlikely.

$$SO_2 + Na_2C_2O_4 = SO + Na_2CO_3 + CO_2 \qquad (3)$$

$$2SO = S + SO_2 \qquad (4)$$

$$S + O_2 = SO_2 \qquad (5)$$

$$SO_2 + Na_2CO_3 = Na_2SO_3 + CO_2 \qquad (6)$$

$$1/2O_2 + Na_2SO_3 = Na_2SO_4 \qquad (7)$$

This made us suspect that the radical[12] $SO_2^{\cdot-}$ was the more likely intermediate that reacts with $O_2$. Its formation would involve a single electron transfer (SET) from the surface of the crystal. A SET mechanism is also consistent with our earlier observation[9] that $Cl_3C–CCl_3$ is formed when $CCl_4$ is passed over

$Na_2C_2O_4$ at a similar temperature (320 °C), since this product is most easily rationalized by recombination of two $CCl_3^{\bullet}$ radicals formed by SET to $CCl_4$. Of course, $CCl_4$ is a different class of substrate, so this may not be relevant.

The $SO_2^{\bullet-}$ radical was previously observed in dithionite solutions by electron paramagnetic resonance.[13] Prior mechanistic studies[14] suggest that air oxidation of dithionite solutions to $SO_4^{2-}$ goes *via* the pathway of eqn. (8)–(10).

$$S_2O_4^{2-} = 2SO_2^{\bullet-} \tag{8}$$

$$O_2 + SO_2^{\bullet-} = SO_4^{\bullet-} \tag{9}$$

$$SO_4^{\bullet-} + SO_2^{\bullet-} = SO_4^{2-} + SO_2 \tag{10}$$

Our data are consistent with a similar mechanism operating in the sodium oxalate reaction. If so, it is an unusual case of an $O_2$ oxidation where the substrate and not $O_2$ is reductively activated.

## Conclusions

In this paper, we describe a simple thermal method for the reduction of $SO_2$ to $S_8$ using hot sodium oxalate. When the reaction was used for the removal of $SO_2$ from air mixtures, we found that oxidation of $SO_2$ to $Na_2SO_4$ took place instead of reduction to $S_8$. A mechanism is discussed.

## Experimental

### Reduction of sulfur dioxide

***Trap to trap multipass (TM) or single pass (SP) experiment***

The apparatus, consisting of a glass tube wrapped with a heating tape, was connected either to a pair of cold traps on each end (TM) or to the gas source *via* a flow meter (SP) and loaded with powdered sodium oxalate (40.0 g, 298.5 mmol). The substrate was passed (70 mL min$^{-1}$ for 2.5 h) through the heated (370 °C) oxalate bed (SP) or passed through the oxalate bed (70 mL min$^{-1}$ for 2.5 h) and condensed in the trap (TM) and subsequently passed from trap to trap by heating the source trap and cooling the sink trap (acetone/dry ice, −78 °C).

The unreacted sodium oxalate was determined by titration with 0.15 M $KMnO_4$. Sulfur (0.85 g, 26.56 mmol) was isolated from the bed by extraction with carbon disulfide to constant weight. Sodium sulfite (6.69 g, 51.08 mmol) was also found in the bed which was determined by titration with 0.2 M $NaI_3$ solution and the sodium sulfate thus formed was determined gravimetrically using $BaCl_2$. Only three passes were required to convert the full sample (5.23 g, 81.72 mmol, 95%) into sulfur and sodium sulfite.

### Attempted reaction with oxygen

A flow of $O_2$ (33.3 ml h$^{-1}$) was passed through a $Na_2C_2O_4$ bed (40.0 g, 298.5 mmol) at 370 °C. After 3 h flow, the $Na_2C_2O_4$ in the bed was determined by titration with 0.15 M $KMnO_4$ solution showing that no reaction had occurred. We repeated this experiment, but after 3 h, the $O_2$ flow was closed and a flow of $SO_2$ (10 ml min$^{-1}$) was passed through the bed. After a few minutes, condensation of $S_8$ was observed in the air cooled condenser placed at the exit of the bed. This indicates, that at the temperature of eqn. (3), $SO_2$ was reduced to $S_8$, while $O_2$ did not react with the bed.

### Reaction with sulfur dioxide and dry air

***Single pass (SP) experiment***

Sodium oxalate (40.4 g, 301.9 mmol) was placed in the reactor and a 1:1 mixture of $SO_2$ (flow: 14.0 ml min$^{-1}$) and dry air was passed through the hot bed (370 °C) for 10 h. The solid mixture in the bed was dissolved in water and the unreacted sodium oxalate (19.26 g, 143.73 mmol) was determined by titration with 0.15 M $KMnO_4$ solution. The solution failed to react with an aqueous solution of $NaI_3$, indicating the absence of sodium sulfite. However, $Na_2SO_4$ (22.4 g, 158.0 mmol) was found in the bed as determined gravimetrically with $BaCl_2$. We found that one mole of sodium oxalate (21.2 g, 158.0 mmol) was consumed per mole of $Na_2SO_4$ (22.4 g, 158.0 mmol) formed.

### Removal of sulfur dioxide from air

***Single pass experiment***

A stream of dry air (flow 13.7 ml min$^{-1}$) was passed through a dilute solution of $Na_2SO_3$ (0.05 M) which was acidified with an excess of HCl (10 ml $HCl_{(c)}$). The gas stream was then passed through the hot $Na_2C_2O_4$ cylindrical bed (40.0 g, 0.30 molper bed) with the following dimensions: 6.0 cm and 1.7 cm. The removing efficiency increases with the retention time of $SO_2$ in the bed (number of beds used). We measured the results for one, two and three beds. The percentage of $SO_2$ removed was calculated by running identical experiments with cold $Na_2C_2O_4$ bed(s). The $SO_2$ unretained in the bed was trapped in 500 ml solution of $NaI_3$ (0.05 M), reacted with a known ammount of $Na_2SO_3$ and titrated by return with $NaI_3$. The data obtained are reported in Table 1. The average concentration of $SO_2$ in the stream was in the range 1.5–3.0% v/v as determined by measuring the volume of air and the absorbed $SO_2$ in a 0.2 M $NaI_3$ solution.

**Table 1** Removal of $SO_2$ from air

| Number of beds | Length of the bed/cm | % $SO_2$ removed |
|---|---|---|
| 1 | 6 | 60 |
| 2 | 12 | 72 |
| 3 | 18 | 80 |

***Trap to trap multipass experiment in the presence of air***

The apparatus, consisting of a glass tube wrapped with a heating tape, was connected to a pair of cold traps on each end (TM) loaded with powdered sodium oxalate (40.0 g, 298.5 mmol). A mixture of 1:1 $SO_2$/dry air was passed (30 mL min$^{-1}$ for 3.5 h) through the heated (370 °C) oxalate bed. The unreacted $SO_2$ was condensed in the trap (TM) and subsequently passed from trap to trap in a stream of dry air by heating the source trap and cooling the sink trap (acetone/dry ice, −78 °C). The exit of the apparatus was connected to a trap containing 500 ml 0.05 M $NaI_3$ in order to capture the $SO_2$ that escapes from the trap due to imperfect cooling (0.30 g, 4.68 mmol). Unreacted sodium oxalate was determined by titration with 0.15 M $KMnO_4$ and the $Na_2SO_4$ (5.55 g, 39.1 mmol) gravimetrically determined by precipitation with $BaCl_2$, showing that 89% of the $SO_2$ (2.5 g, 39.1 mmol) was retained in the bed.

## Acknowledgment

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## References

1 P. W. Schenk and R. Steudel, *Angew. Chem., Int. Ed. Engl.*, 1965, **77**, 1089.

2 R. J. Lovejoy, J. H. Coldwell, D. F. Eggers and D. G. Halsey, *J. Chem. Phys.*, 1962, **36**, 612.

3 (*a*) G. E. Likens, R. F. Wright, J. N. Galloway and T. J. Butler, *Sci. Am.*, 1979, **241**, 43; (*b*) G. E. Likens, C. T. Driscoll and D. Buso, *Science*, 1996, **272**, 245.

4 *Sulphur Dioxide. Applications in Foods, Beverages and Pharmaceuticals*, L. C. Schroeter, Pergamon Press, Oxford, 1966: (*a*) p. 1; (*b*) p. 39; (*c*) pp. 14–17; (*d*) pp. 41–76.
5 *Sulfur Removal and Recovery from Industrial Processes*, ed. J. B. Pfeiffer, *Adv. Chem. Ser.*, vol. 139, ACS, Washington, DC, 1975.
6 *Inorganic Sulfur Chemistry*, ed. G. Nickless, Elsevier, London, 1968: (*a*) p. 375; (*b*) pp. 405–406.
7 H. J. Frazer and J. W. Kirkpatrick, *J. Am. Chem. Soc.*, 1940, **62**, 1659.
8 (*a*) R. H. Flowers, R. J. Gillespie and E. A. Robinson, *J. Chem. Soc.*, 1963, 2464; (*b*) C. Jacques and J. Leisten, *J. Chem. Soc.*, 1961, 4963; (*c*) R. J. Gillespie and D. J. Millen, *Quart. Rev.*, 1948, **2**, 277; (*d*) D. J. Millen, *J. Chem. Soc.*, 1950, 2600.
9 (*a*) J. Burdeniuc and R. H. Crabtree, *Science*, 1996, **271**, 340; (*b*) L. H. McAlexander, C. M. Beck, J. Burdeniuc and R. H. Crabtree, *J. Fluorine Chem.*, 1999, submitted.
10 (*a*) W. A. Sheppard and C. M. Sharts, *Organic Fluorine Chemistry*, W. A. Benjamin, New York, 1969, p. 450; (*b*) M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, Chichester, 1976, pp. 563–566; (*c*) R. Perry, *Fluorine—The First Hundred Years*, ed. R. E. Banks, D. W. A. Sharp and J. C. Tatlow, Elsevier, New York, 1986, pp. 293–295.
11 *Comprehensive Inorganic Chemistry*, ed. J. C. Bailar, H. J. Emeleus, R. Nyholm and A. F. Trotman-Dickenson, Pergamon Press, 1973, vol. 2, pp. 859–868.
12 W. Hodgson, *Nature*, 1956, **178**, 489.
13 S. Lynn, R. G. Rinker and W. H. Concoran, *J. Phys. Chem.*, 1964, **68**, 2363.
14 R. G. Rinker, T. P. Gordon, D. M. Manson, R. R. Sakaida and W. H. Corcoran, *J. Phys. Chem.*, 1960, **64**, 573.

*Paper 9/00393B*

# Hydrolysis and saponification of methyl benzoates

## A green procedure in high temperature water

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## Summary

We report a study of the hydrolysis and saponification of methyl benzoates, **1**, in both water and slightly alkaline solution (2% KOH) at high temperature (200–300 °C). In this green, solvent-free procedure, we achieve partial hydrolysis or quantitative saponification of sterically hindered and *p*-substituted methyl benzoatesin 30 min. In addition, methyl 2,4,6-trimethylbenzoate, **1a**, and methyl *p*-aminobenzoate, **1g**, can be selectively decarboxylated or hydrolyzed by changing the temperature and/or pH of the reaction medium. The enhancement of the nucleophilicity of diluted alkaline solution at high temperature is proved by the quantitative hydrolysis of the sterically hindered ester, **1a**, and the partial hydrolysis of the trifluoromethyl group to a carboxylic acid in methyl *p*-trifluoromethylbenzoate, **1e**.

## Introduction

Over the past five years, the study of the reactivity of simple molecules in high temperature water (HT-$H_2O$) has led to the development of solvent-free synthetic procedures in organic chemistry.[1–4] The application of these procedures to industrial processes will lead to a new environmentally friendly 'green technology', with minimised waste problems. This research has been encouraged by the change of the physical and chemical properties of water from room temperature to supercritical (374 °C). For instance, the decrease of the relative permittivity of water implies an increasing solubility of the organic compounds,[5,6] and the increase of its dissociation constant[7] can promote acid–base catalysed reactions that do not take place at lower temperatures. An example is the hydrolysis of carboxylic esters in HT-$H_2O$,[1,2] which has been applied to the hydrolysis of vegetable oils.[8]

Hydrolysis of carboxylic esters in water is a two-phase reaction and rates are usually slow due to the low solubility of the esters in the reaction medium. Although several procedures have been developed to overcome this problem, including phase transfer catalysis[9,10] and ultrasound,[11] they present serious disadvantages due to high costs and the toxicity of solvents and catalysts. HT-$H_2O$ seems to be an environmentally friendly alternative. However, only partial hydrolysis of carboxylic esters has been achieved in most examples so far.[2,3] Hydrolysis in HT-$H_2O$ is a process acid-catalysed by the formation of soluble carboxylic acids during the reaction, which eventually reaches equilibrium. In contrast, hydrolysis in basic medium is highly effective because of the formation of a carboxylate ion, which continuously shifts the reaction to the hydrolysed side. Hence, hydrolysis in HT-$H_2O$ could be improved by performing the reaction under basic conditions and, so far, the saponification of carboxylic esters at high temperatures has not been studied.

We report a fundamental study of the hydrolysis and saponification of methyl benzoates, **1**, in $H_2O$ and slightly alkaline solution at high temperature. We have verified the efficacy of the media in the difficult hydrolysis of sterically hindered esters, such as methyl 2,4,6-trimethylbenzoate (**1a**), as well as the stability and influence on the rate of hydrolysis of other functional groups in the molecule.

## Results and discussion

### Hydrolysis in high temperature water

Water in the temperature range 250–300 °C promotes hydrolysis of methyl benzoates, **1** (Scheme 1), recovering unreacted **1** at temperatures of 200 °C or below. The results are summarised in Table 1.

HT-$H_2O$ is a powerful system able to hydrolyse sterically hindered esters such as **1a**, which usually undergoes acid hydrolysis only under extreme conditions, *e.g.* in concentrated $H_2SO_4$ solution.[12] However, decarboxylation of **2a** is a secondary reaction in both $H_2SO_4$ and HT-$H_2O$. Thus, the reaction of **1a** at 250 °C yielded the acid **2a** (20%) after 0.5 h, and a mixture of **2a** (53%) and 1,3,5-trimethylbenzene **3a** (20%) after 2 h. Reaction at 300 °C for 0.5 h gave only **3a** (89%). These results indicate that hydrolysis and decarboxylation are competitive processes at 250 °C while decarboxylation is more favoured at 300 °C.

### Green Context

**Reactions in high temperature water represent a potentially green methodology. They avoid the extreme conditions required for supercritical water, but the high temperatures used (>200 °C) are sufficient to render the water non-polar enough to allow good solubility of many organic compounds. This contribution describes the reactions of methyl esters of aromatics in this fascinating medium. Depending on the exact conditions chosen, the methyl esters either hydrolyse to give the acids (basic conditions), or hydrolyse and decarboxylate (neutral conditions).** ***DJM***

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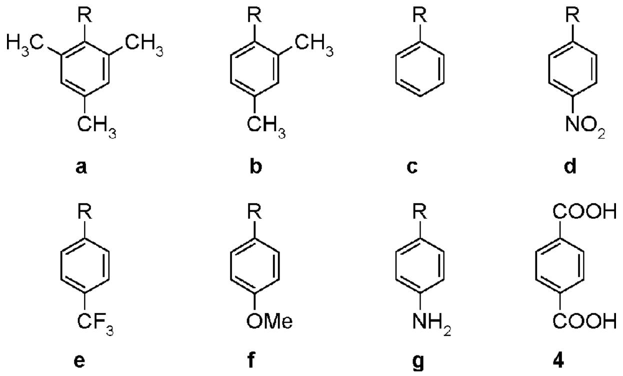

**1** R = COOMe; **2** R = COOH; **3** R = H

**Scheme 1**

**Table 1** Hydrolysis of methyl benzoates **1** in HT-water[a]

| Entry | Substrate | *T*/°C | Conversion (%)[b] | Product(s) (yield(%))[c] |
|---|---|---|---|---|
| 1 | **1a** | 250 | 21 | **2a** (20) |
| 2 | **1a** | 250[d] | 73 | **2a** (53) + **3a** (20) |
| 3 | **1a** | 300 | 100 | **3a** (89) |
| 4 | **2a** | 250[d] | 50 | **3a** (40) |
| 5 | **2a** | 250[d,e] | 80 | **3a** (76) |
| 6 | **1b** | 250 | 30 | **2b** (28) |
| 7 | **1c** | 250 | 60 | **2c** (59) |
| 8 | **1d** | 250 | 74 | **2d** (66) |
| 9 | **1e** | 250 | 65 | **2e** (64) |
| 10 | **1f** | 250 | 56 | **2f** (46) |
| 11 | **1f** | 300 | 80 | **2f** (70) + **3f** (4) |
| 12 | **1g** | 250 | 62 | **2g** (7) + **3g** (51) |

[a] $H_2O$ and **1** (or **2**) were reacted for 0.5 h. Products were isolated by acid–base extraction and identified by GC and/or NMR spectra, in comparison with authentic samples. [b] Isolated. [c] Gravimetric yield based on starting substrate. [d] Reaction for 2 h. [e] Added $CO_2$ (10 bar, 20 °C).

Furthermore, the increase of the acidity of the water due to the $CO_2$ evolved[13] catalyses the decarboxylation process. Thus, reaction of the acid **2a** in $H_2O$ at 250 °C for 2 h underwent 50% decarboxylation, and increased up to 80% by performing the reaction under an added pressure of $CO_2$ (10 bar at 20 °C).

As shown in the following experiments, steric factors rather than polar ones control the rate of hydrolysis in HT-$H_2O$. Therefore, the nature of the substituent *para* to the ester group has less effect on the rate than the presence of *ortho* groups. Furthermore, reduced hindrance of the ester moiety disfavours its decarboxylation. Thus, methyl 2,4-dimethylbenzoate **1b** underwent hydrolysis to **2b** (28%) at 250 °C for 0.5 h without formation of xylene and *p*-benzoates **1c**, **1d**, **1e** and **1f** underwent hydrolyses (56–74%) under the same reaction conditions to the acids **2c**, **2d**, **2e** and **2f**. However, amino-benzoate, **1g**, gave largely aniline, **3g**. This is not unexpected considering that acid-catalysed decarboxylation can also be favoured by electron-releasing groups like $NH_2$. However, the methoxy group in **1f** is not powerful enough to induce decarboxylation and only by forcing the reaction conditions (300 °C) was it possible to detect a small amount of anisole **3f**.

Although $-NH_2$, $-OCH_3$, $-NO_2$ and $-CF_3$ groups are stable under the reaction conditions, their stability decreases with increasing temperature. Thus, the nitro-ester **1d** decomposed at temperatures above 300 °C. In contrast to previous results,[2,3] no significant cleavage of the methoxy group was observed for the methoxybenzoate, **1f**, neither at 250 nor even at 300 °C.

Finally, acid catalysis for the hydrolysis of carboxylic esters in HT-$H_2O$ has been explained by the formation of soluble carboxylic acids during the reaction.[2,3] However, the temperature dependence of $K_w$ plays a major role. As will be shown in the following section, basic hydrolysis occurs readily at only 200 °C. Therefore, if no hydrolysis is observed for a particular compound in HT-$H_2O$ at 200 °C, the value of $K_w$ must be too low to catalyse the hydrolysis, rather than a problem of solubility.

## Saponification in alkaline water at high temperature

Slightly alkaline $H_2O$ (2% KOH) promotes hydrolysis of methyl benzoates **1** in the temperature range 200 to 300 °C, even though there is little conversion of **1** at ≤ 150 °C. The results are summarised in Table 2.

**Table 2** Saponification of methyl benzoates **1** in HT-alkaline $H_2O$ (2 % KOH)[a]

| Entry | Ester | *T*/°C | Conversion (%)[b] | Product(s) (yield (%))[c] |
|---|---|---|---|---|
| 1 | **1a** | 200 | 17 | **2a** (15) |
| 2 | **1a** | 200[d] | 30 | **2a** (28) |
| 3 | **1a** | 250 | 60 | **2a** (57) |
| 4 | **1a** | 300 | 100 | **2a** (90) |
| 5 | **1b** | 200 | 36 | **2b** (35) |
| 6 | **1b** | 250 | 81 | **2b** (79) |
| 7 | **1b** | 300 | 100 | **2b** (90) |
| 8 | **1c** | 200 | 100 | **2c** (98) |
| 9 | **1d** | 200 | 100 | **2d** (88) |
| 10 | **1e** | 200 | 100 | **2e** (98) |
| 11 | **1e** | 375[e] | 100 | **2e** (41) + **4** (20) |
| 12 | **1f** | 200 | 92 | **2f** (90) |
| 13 | **1f** | 200[f] | 98 | **2f** (87) |
| 14 | **1f** | 220[g] | 97 | **2f** (86) |
| 15 | **1g** | 200 | 100 | **2g** (84) |

[a] 2% KOH (aq) and **1** were reacted for 0.5 h. Products were isolated by acid–base extraction and identified by GC and/or NMR spectra, in comparison with authentic samples. [b] Isolated **1**. [c] Gravimetric yield based on starting **1**. [d] Reaction for 2 h. [e] Black solid from thermal decomposition. [f] 3 M $NH_4OH$ (aq). [g] 2% $Na_2CO_3$ (aq).

HT-alkaline $H_2O$ is an efficient medium to hydrolyse hindered esters like **1a**. Thus, **1a** underwent hydrolysis to the acid **2a** at 200, 250 and 300 °C in 17, 60 and 100% conversion, after only 0.5 h, without detectable decarboxylation. This relative high reactivity of **1a** at 300 °C is surprising. Indeed, **1a** is so difficult to hydrolyse, owing to its steric hindrance, that its hydrolysis is a classical test for evaluating the ability of a basic system to act as a strong nucleophile. Thus, hydrolysis of **1a** has only been achieved with strongly nucleophilic reagents like ‘anhydrous hydroxide,’[14] *n*-propyllithium[15] or ‘solid KOH–Aliquat 336 system.’[10] Furthermore, **1a** can not be hydrolysed in 20% NaOH (aq) neither after 1.5 h reflux nor after 1 h application of ultrasound, used to increase the ester solubility in water.[11] Therefore, alkaline $H_2O$ at 200–300 °C is an outstanding nucleophilic system. Proof of this is the hydrolysis of the $CF_3$ group to COOH at 375 °C (*i.e.* under supercritical conditions) when terephthalic acid **4** was isolated in 20% yield in the reaction of trifluoromethyl ester **1e**.

In contrast to the low reactivity of **1a**, **1b** underwent 36% conversion and **1c** was hydrolyzed quantitatively at 200 °C in 0.5 h. Also saponification of *p*-substituted esters **1d**, **1e**, **1f** and **1g** was quantitative under the same conditions. Their higher reactivity can be explained again in terms of hindrance on the COOMe moiety. As a control, the hydrolysis of **1f** was performed in 3 M $NH_4OH$ (aq) and 2% $Na_2CO_3$ (aq) at 200 °C for 30 min, obtaining identical results to those for 2% KOH (aq).

## Conclusions

In summary, water or alkaline solution at high temperature provides an excellent medium for the green and selective hydrolysis, or decarboxylation when possible, of methyl benzoates **1**. Decarboxylation takes place in HT-$H_2O$ on sterically hindered esters or esters with electron-releasing groups like **1a** or **1g**. Alkaline HT-$H_2O$ is a powerful nucleophilic system, more efficient than HT-$H_2O$ for hydrolysis of carboxylic esters. The sterically hindered ester **1a** is efficiently hydrolysed without decarboxylation.

## Experimental

### Materials

Methyl benzoates **1c**, **1d**, **1e**, **1f** and **1g** (Aldrich or Lancaster) were used as received. Methyl esters **1a** and **1b** were prepared by reaction of the corresponding carboxylic acid **2** with methanol, 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).[16] Water was purified by standard procedures.

### Analysis

Reaction products were identified by GC and NMR spectra, in comparison with authentic samples. GC analysis were performed on a non-polar capillary column [EC-5 (SE-54), Alltech, 30 m, film thickness 0.25 μm, I.D. 0.32 mm].

### High pressure/temperature batch reactor system

*SAFETY WARNING: These reactions involve high pressures and must only be carried out in an apparatus with the appropriate pressure rating at the reaction temperature*. Reactions were carried out in a batch reactor system consisting of a reactor vessel connected to a shut-off valve *via* a pressure transducer (Fig. 1).

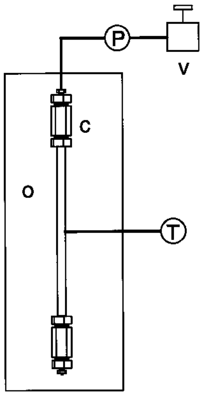

**Fig. 1** Schematic view of the high *T/p* batch reactor system. The components are labelled as follows: **C**, high pressure vessel; **O**, high temperature oven; **P**, pressure monitor; **T**, thermocouple; **V**, high pressure valve.

The high temperature/pressure stainless steel 316 reactor vessel (0.9 cm O.D., 0.5 cm I.D., 5.2 ml internal volume, Keystone Scientific Inc.) had a maximum pressure rating of 690 bar at 400 °C. A chromel/alumel thermocouple monitored the temperature of the reactor wall. The pressure transducer (RDP electronics) had a pressure rating of 690 bar. The batch reactor was heated in an oven (PYE series 104). Overpressure could be avoided by releasing the pressure through the shut-off valve (HIP). No visible corrosion of the vessel was observed at the operating conditions.

### General procedure

The reaction vessel was leak-tested with $N_2$, charged with the appropriate amount of $H_2O$ and reagents, sealed, placed in the oven, and connected to the pressure transducer and thermocouple. Reaction time was measured from the moment that the reaction temperature was reached and does not include the time required to reach the reaction temperature or to cool the system (10–15 min each). The appropriate amount of $H_2O$ was calculated for each temperature considering the density of the liquid as follows: $\rho_w$ = mass of $H_2O$/vessel volume. *Safety: The maximum amount of water which could be safely loaded without overpressure was calculated from the steam tables.*[17] Reactions were performed at liquid densities of the fluid (0.7–0.9 g $cm^{-3}$).

### Saponification/hydrolysis of methyl benzoates 1

Reactions were performed in $H_2O$ and in 2% KOH aqueous solution. The reaction vessel was charged with $H_2O$ (3.7–4.7 ml) and ester **1** (1.0–1.5 mmol). The system was heated for 0.5–2 h at 150–300 °C. The work-up of the reaction consisted of acid-base extraction of the aqueous reaction mixture with an organic solvent (methylene chloride or diethyl ether) and/or filtration of the carboxylic acid **2**. The reaction products were analysed by NMR and yields determined gravimetrically.

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## References

1 J. An, L. Bagnell, T. Cablewski, C. Strauss and R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505.
2 A. R. Katritzky, S. M. Allin and M. Siskin, *Acc. Chem. Res.*, 1996, **29**, 399.
3 B. Kulmann, E. M. Arnett and M. Siskin, *J. Org. Chem.*, 1994, **59**, 3098.
4 M. B. Korzenski and J. W. Kolis, *Tetrahedron Lett.*, 1997, **38**, 5611.
5 J. F. Connoly, *J. Chem. Eng. Data*, 1966, **11**, 13.
6 E. U. Franck, *J. Chem. Thermodyn.*, 1987, **19**, 225.
7 W. L. Marshall and E. U. Franck, *J. Phys. Ref. Data*, 1981, **10**, 295.
8 R. L. Holliday, J. W. King and G. R. List, *Ind. Eng. Chem. Res.*, 1997, **36**, 932.
9 N. Dehmlow, *J. Chem. Res. (S)*, 1979, 238.
10 A. Loupy, M. Pedoussaut and J. Sansoulet, *J. Org. Chem.*, 1986, **51**, 740.
11 S. Moon, L. Duchin and J. V. Cooney, *Tetrahedron Lett.*, 1979, **41**, 3917.
12 H. P. Treffers and L. P. Hammett, *J. Am. Chem. Soc.*, 1937, **59**, 1708.
13 K. L. Toews, R. M. Shroll and C. M. Wai, *Anal. Chem.*, 1995, **67**, 4040.
14 P. Gassman and W. N. Schenk, *J. Org. Chem.*, 1977, **42**, 918.

15 C. Lion, J.-E. Dubois, J. A. MacPhee and Y. Bonzougou, *Tetrahedron*, 1979, **35**, 2077.
16 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
17 J. H. Keenan, F. G. Keyes, P. G. Hill and J. G. Moore, *Thermodynamic properties of water including steam tables*, J. Wiley & Sons, New York, 1969.

*Paper 8/09670H*

# Friedel–Crafts acylation using sulfated zirconia as a catalyst

## Acylation of benzene with 4-chlorobenzoyl chloride over sulfated zirconia as catalyst

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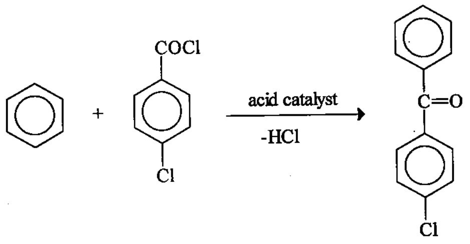
## Summary

Synthesis of fine chemicals and intermediates by using Friedel–Crafts acylations is an important process in organic chemical technology. In most cases, very good yield and selectivity can be obtained with aluminium chloride as catalyst in conjunction with nitrobenzene as solvent. However, with modern environmental restrictions, in consonance with green chemistry, replacement of aluminium chloride–nitrobenzene or $BF_3$–HF with solid catalysts has great industrial relevance. Acylation of benzene with 4-chlorobenzoyl chloride was attempted with different solid acid catalysts such as dodecatungstophosphoric acid (DTPA), DTPA/K-10 clay, K-10, Amberlite, Amberlyst-15, Indion-130, Filtrol-24 clay, and sulfated zirconia. However, only sulfated zirconia was found to be effective leading to 100% selective formation of 4-chlorobenzophenone, which is useful as an organic and pharmceutical intermediate; for instance, in the manufacture of Cytrazin—a well known drug. The kinetics of the reaction was studied to establish that the reaction obeys the Langmuir–Hinshelwood–Hougen–Watson mechanism with very weak adsorption of the reactants. The reaction is intrinsically kinetically controlled.

## Introduction

Acylation of benzene with 4-chlorobenzoyl chloride gives products which are important in the pharmaceutical and fine chemical industries. An important drug, Cytrazin, is manufactured from the acylated product of 4-chlorobenzophenone. The most common method of introducing an acyl group into an organic compound is *via* Friedel–Crafts acylation by using either aluminium chloride in nitrobenzene or boron trifluoride in liquid HF as catalyst.[1,2] Various other Lewis acids such as $FeCl_3$, $ZnCl_2$, $SnCl_4$, $InCl_4$ and $SbCl_5$, and Brønsted acids, such as $H_2SO_4$ and HCl have been studied extensively.[3] As a consequence, the major drawback of Friedel–Crafts acylation on the industrial scale consists of serious effluent problems. In our laboratory, we have been seeking new methods to replace the use of strongly acidic, homogeneous, corrosive and polluting catalysts and processes in a variety of industries such as refineries, petrochemicals, pharmaceuticals and drugs, rubber chemicals, dyestuffs, agrochemicals, perfumery and flavour chemicals, with environmentally benign heterogeneous solid acid catalysts and processes.[4–20] The current work addresses one such commercially important process of preparing 4-chlorobenzophenone, for which the efficacy of different solid acid catalysts is evaluated.

4-Chlorobenzophenone is routinely prepared by employing 4-chlorobenzoyl chloride and benzene with $AlCl_3$ as catalyst.



**Scheme 1**

There are some reports on the reaction between chlorobenzene and benzoyl chloride in the presence of bismuth(III) triflate to produce the target compound.[21] (Trichloromethyl)benzene is also used as an acylating agent with aromatics in 1,2-dichloroethane in the presence of $AlCl_3$ to give the corresponding benzoyl derivatives.[22]

In this paper, we would like to communicate the details of our investigation of acylation of benzene with 4-chlorobenzoyl chloride where the activities of different solid acid catalysts such as K-10 clay, Filtrol-24 clay, dodecatungstophosphoric acid (DTPA), DTPA supported on K-10, Amberlyst-15, Amberlite IR 120, Indion-130 and sulfated zirconia are tested and a kinetic model built.

### Green Context

**The efficient catalytic acylation of aromatics *via* the Friedel–Crafts reaction remains a major challenge for clean technology. Traditional methods rely on the use of stoichiometric quantities of 'catalyst'. This article relates to the development of an effective catalyst for one example of this reaction, the synthesis of a pharmaceutical intermediate. Of several materials used, only sulfated zirconia showed good activity. While the reaction still requires the use of the acid chloride (better would be the acid itself), this work represents a significant advance in the search for genuinely active Friedel–Crafts acylation catalysts. *DJM***

# Experimental

## Chemicals and catalysts

K-10 and Filtrol-24 were obtained from Fluka. Indion-130, an ion exchange resin, was obtained from M/s. Ion Exchange (India) Ltd. Amberlyst-15 and Amberlite IR 120, both ion exchange resins, are products of Rohm and Hass. Zirconium oxychloride, dodecatungstophosphoric acid and benzene were obtained from M/s. s.d. Fine Chemicals Ltd., Mumbai, India. 4-Chlorobenzoyl chloride was obtained from Merck Ltd. All chemicals were analytical grade reagents and were used without further purification. The catalysts used for the reaction were dried at 100°C under vacuum for 6 h before use. Dodecatungstophosphoric acid (DTPA)/K-10 was prepared by a well established procedure in our laboratory.[14]

Sulfated zirconia was also prepared by an established procedure in our laboratory,[4,5,17] adding aqueous ammonia solution to zirconium oxychloride solution at a pH of 10. The precipitate was throughly washed with distilled water and freed from ammonia and chloride ions. It was dried in an oven at 120 °C for 24 h. The sulfation of the zirconia was done using 15 ml $g^{-1}$ of 0.5 M sulfuric acid. It was dried at 110 °C and calcined at 650 °C for 3 h.

## Reaction procedure

The reactor consisted of a flat-bottomed cylindrical glass vessel of 150 ml capacity equipped with four baffles, a turbine stirrer and a condenser. The assembly was kept in an isothermal oil bath at a known temperature and mechanically agitated with an electric motor. A typical reaction mixture consisted of 0.02 moles of 4-chlorobenzoyl chloride and 0.2 moles of benzene with 10 wt% of the catalyst. The total weight of the reaction mixture was 19.10 g. The reaction was carried out at 70 °C at a speed of agitation of 800 rpm. HPLC analysis was performed (Model: Toscho, UV-8010) by using a Merck 50983 column with a stationary phase of Lichrospher 100 RP-18, particle size 5 μm, prepacked on a 250 × 4 mm i.d. column with a Tosoh UV-8010 detector set at 272 nm. The eluent used for the analysis was HPLC grade methanol with a flow rate of 1.0 ml $min^{-1}$.

## Identification and isolation of product

The reaction mixture was filtered to remove the solid catalyst and the various products were isolated. Confirmation of the products was done through melting point, GC, TLC and $^1H$ NMR spectroscopy by comparison with the standard products. It was found that the selectivity was 100% towards the product formed. Typically the product was isolated from the reaction mixture after 5h. The catalyst was filtered out, benzene removed by evaporation in a rotary evaporator, and the solid mass tested with thin layer chromatography (TLC). Benzene and silica gel were used for the TLC and also for column chromatography. The isolated product was analysed by melting point and $^1H$ NMR analysis. The keto derivative of the product was also prepared and analysed as a confirming test. All tests confirmed that the product formed in the reaction was 4-chlorobenzophenone.

# Results and discussion

## Effect of various catalysts

The efficacy of different catalysts was evaluated at 70 °C under otherwise similar conditions in the absence of any internal and external diffusional resistance. The catalysts used were dodecatungstophosphoric acid (DTPA), 20% DTPA/K10, K10, S-$ZrO_2$, Amberlyst-15, Amberlite IR 120 and Indion-130. Apart from S-$ZrO_2$, none of the catalysts was found to catalyse the reaction.

The ion-exchange resins Amberlyst-15, Amberlite IR 120 and Indion 130 are all Bronsted acids and seem to be ineffective. Heteropoly acids also did not catalyse the reaction because they do not have enough strength to form carbenium (carbo-cation) ions of the acylating species.

The acylation requires very strong acids and, apart from S-$ZrO_2$ and $AlCl_3$, the other acids were very ineffective. Sulfated zirconia is an intriguing very strong solid acid having both Brønsted and Lewis acid sites, and its acidity is a subject matter of great research.[23,24] The catalyst has been well characterised.[23–25] A possible reaction mechanism explaining the efficacy of this catalyst is shown in Fig. 1.

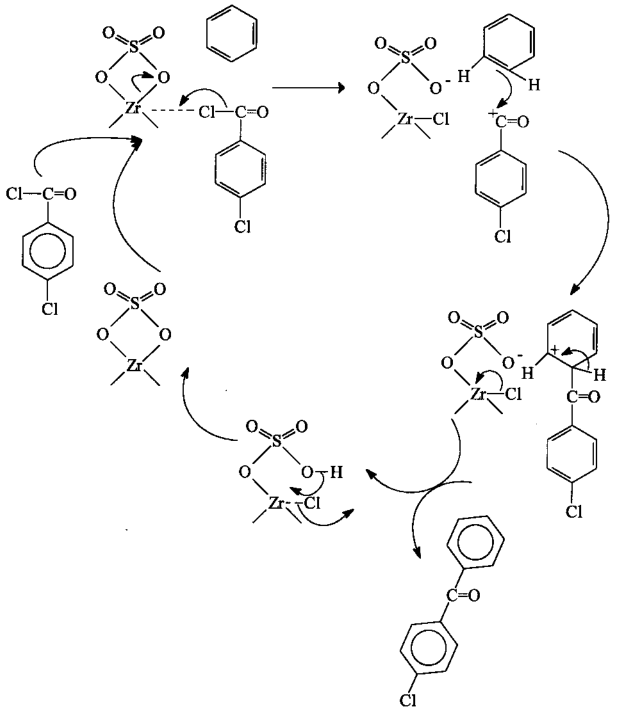


**Fig. 1** Reaction mechanism over sulfated zirconia.

Further experiments were conducted with S-$ZrO_2$ as catalyst. In order to assess the role of external mass transfer, the effect of the speed of agitation was studied. Conversions reported in all figures are based on the limiting reactant 4-chlorobenzoyl chloride. Since the selectivity to the desired product was 100% at all conversions, these conversions are also the yields of the product based on the initial amount of 4-chlorobenzoyl chloride taken for reaction.

# Effect of speed of agitation

Since benzene (reactant B) was used in large molar excess over 4-chlorobenzoyl chloride (reactant A), there was the likelihood of external resistance for the transfer of the latter from the bulk liquid phase to the external surface of the catalyst particle. Therefore, the speed of agitation was varied under otherwise similar conditions.

The effect of the speed of agitation on the rate of the reaction was studied over 600–1000 rpm. The conversion of 4-chlorobenzoyl chloride at different intervals of time is shown in Fig. 2. There was no significant change in the conversion patterns beyond 800 rpm. This implies that there was no resistance to external mass of transfer of 4-chlorobenzoyl chloride to the external surface of the catalyst. All further reactions were conducted at 800 rpm.

According to the model used for this analysis, the liquid diffusivity values $D_{AB}$ (4-chlorobenzoyl chloride in benzene) and $D_{BA}$ (benzene in 4-chlorobenzoyl chloride) were required, and these

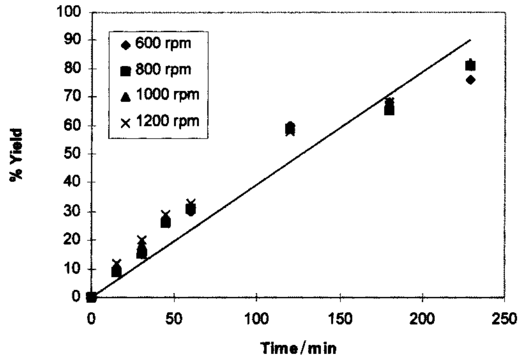


**Fig. 2** Effect of speed of agitation (benzene:4-chlorobenzoyl chloride = 10:1, *T* = 70 °C, catalyst = S-ZrO$_2$, catalyst loading = 10% w/w).

values were calculated by using the Wilke–Chang equation.[9] The values of $D_{AB}$ and $D_{BA}$ at 70°C were calculated as 5.058 × $10^{-5}$ and 3.837 × $10^{-5}$ cm$^2$ s$^{-1}$, respectively.

## Effect of catalyst loading

The effect of catalyst loading was studied at three different loadings varied from 5% to 15% w/w of the total mass of the reaction mixture (Fig. 3). The conversion increases with increasing catalyst loading which is obviously due to the proportional increase in the number of active sites.

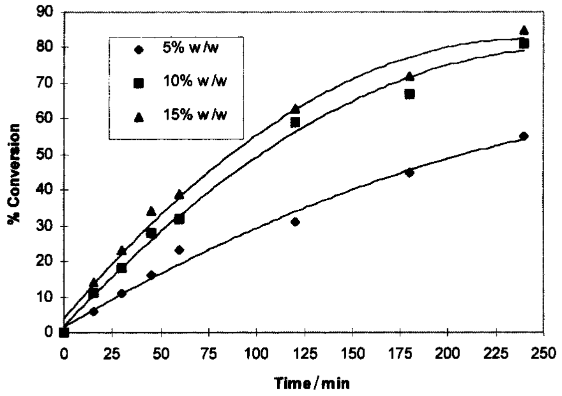


**Fig. 3** Effect of catalyst (benzene:4-chlorobenzoyl chloride = 10:1, speed of agitation = 800 rpm, catalyst = S-ZrO$_2$, *T* = 70 °C).

Furthermore, a plot of initial rate of reaction against catalyst loading, *w*, was made as shown in Fig. 4. This plot is linear thereby indicating that the rate is proportional to the number of active sites present on the surface.

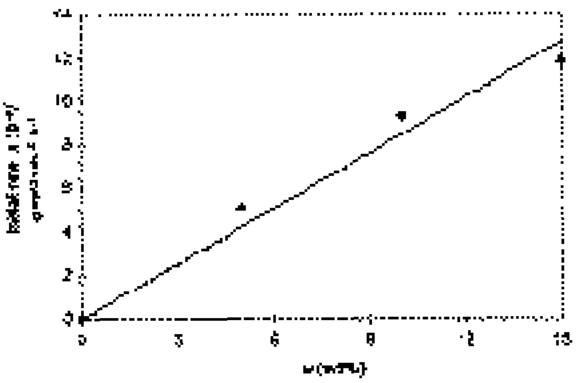


**Fig. 4** Plot of initial rate *vs.* catalyst loading.

## Effect of particle size

The effect of the average particle size of the catalyst on the reaction rate was studied in the ranges of 75 to 225 μm by keeping the same catalyst loading and the results are shown in Fig. 5. It is observed that particle sizes below 90 μm had no effect on the reaction rates. This in turn suggests that intra-particle mass transfer resistance is absent below catalyst particle sizes of 90 μm and the surface reaction is rate controlling, *i.e.* the reaction is intrinsically kinetically controlled.

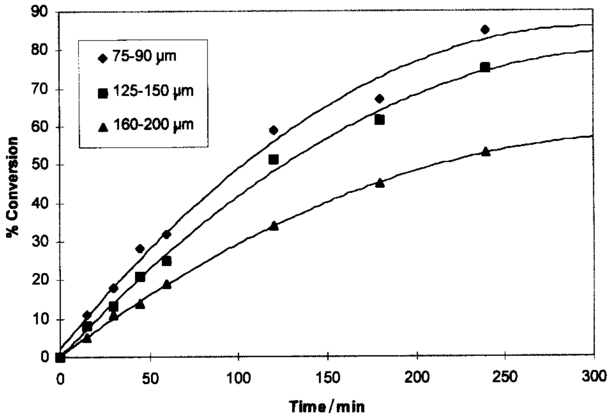


**Fig. 5** Effect of particle size (benzene:4-chlorobenzoyl chloride = 10:1, speed of agitation = 800 rpm, catalyst = S-ZrO$_2$, catalyst loading = 10% w/w), *T* = 70 °C.

## Effect of mole ratio

The effect of the mole ratio of the reactants was studied at benzene : 4-chlorobenzoyl chloride = 1:1 to 10:1 at constant volume. The total volume of the reaction mixture was maintained constant (21 ml) (Fig. 6). The conversion of 4-chlorobenzoyl chloride at mole ratios of benzene to 4-chlorobenzoyl chloride of 1:1, 5:1 and 10:1 were found to be 11, 35 and 81%, respectively, at 70 °C. The conversion was found to increase with increasing benzene concentration. Therefore, all the reactions were conducted at a mole ratio of 10:1 without any solvent, where benzene itself acts as a solvent.

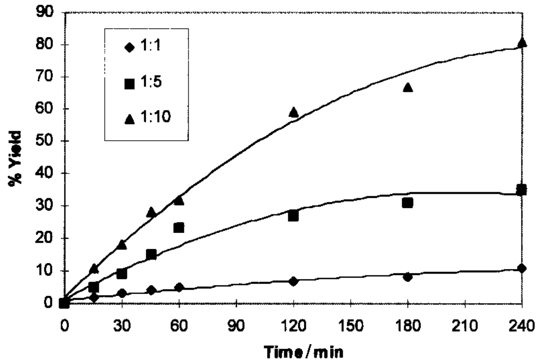


**Fig. 6** Effect of mole ratio (speed of agitation = 800 rpm, catalyst = S-ZrO$_2$, *T* = 70 °C, catalyst loading = 10% w/w).

## Effect of temperature

The reaction was studied at three different temperatures in the range of 50 °C to 70 °C (Fig. 7). The conversion was found to increases substantially with increasing temperature, which suggested that the reaction was kinetically controlled and the activation energy values should be determined.

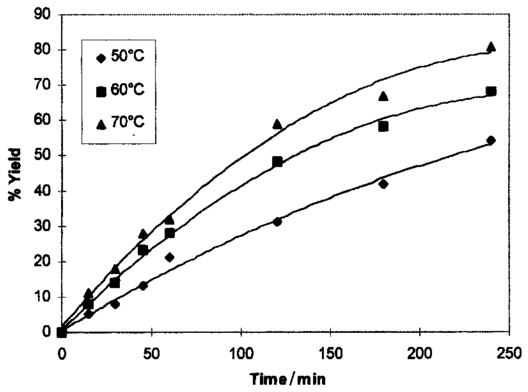


**Fig. 7** Effect of temperature (benzene:4-chlorobenzoyl chloride = 10:1, speed of agitation = 800 rpm, catalyst = S-ZrO$_2$, catalyst loading = 10% w/w).

## Reaction mechanism and kinetics

When the initial rate data are analysed, the overall rate in gmol cm$^{-3}$ s$^{-1}$ can be written as :

$$r_o = k_{SL\text{-}A}a_p\{C_{Ao} - C_{AS}\} = \text{rate of mass transfer of A} \qquad (1a)$$

$$zk_{SL\text{-}B}a_p\{C_{Bo} - C_{BS}\} = \text{rate of mass transfer of B} \qquad (1b)$$

$$\eta k_{R2}wC_{AS}C_{BS} = \text{rate of reaction} \qquad (1c)$$

where $k_{SL\text{-}A}$, $k_{SL\text{-}B}$, $a_p$, $z$ and $\eta$ are the solid–liquid mass transfer coefficients for A and B, the particle surface area per unit liquid volume, the stoichiometric coefficient of B, and the effectiveness factor, respectively.

From eqn. (1a)–(1c) it is possible to get the overall rate. If $C_{Bo} > C_{Ao}$, then

$$r_o = \{(k_{SL\text{-}A}a_p)^{-1} + (\eta k_{R2}wC_{Bo})^{-1}\}^{-1}\, C_{Ao} \qquad (2)$$

That is, we can compare the rate of mass transfer with the rate of reaction ($k_{SL\text{-}A}a_pC_{Ao}$ against $\eta k_{R2}wC_{Bo}C_{Ao}$).

The initial rate of reaction for the slurry reaction, $r_o$ (gmol cm$^{-3}$ s$^{-1}$) can be calculated from the conversion profile of species A (= $C_{Ao}$ d$X_A$/d$t$), and can be compared with the rate of mass transfer of A. As stated earlier, the values of solid–liquid mass transfer coefficients $k_{SL\text{-}A}$ and $k_{SL\text{-}B}$ were calculated by the Sherwood number correlation. To be on the safer side, the limiting value of the Sherwood number was taken as 2. The actual value is $\gg$ 2 due to intense agitation.

Thus, the Sherwood number, Sh,

$$\text{Sh} = k_{SL}d_p/D = 2 \qquad (3)$$

Thus, the $k_{SL\text{-}A}$ and $k_{SL\text{-}B}$ values were calculated as 4.5 × 10$^{-3}$ and 3.4 × 10$^{-3}$ cm s$^{-1}$. The surface area of a particle per unit liquid volume was calculated for 90 μm particle size from

$$a_p = 6w/\rho_p d_p \qquad (4)$$

This value was 3.37 cm$^{-1}$ at a catalyst loading of 9.09 × 10$^{-3}$ g cm$^{-3}$.

Thus, the values of mass transfer rates of A and B from the bulk liquid to the external surface of the catalysts, $k_{SL\text{-}A}\,a_pC_{Ao}$ and $k_{SL\text{-}B}a_pC_{Bo}$ were typically found to be 1.60 × 10$^{-5}$ and 1.20 × 10$^{-5}$ gmol cm$^{-3}$ s$^{-1}$, respectively at a mole ratio A:B of 1:1. The initial observed rate of reaction was found to be 1.05 × 10$^{-7}$ gmol cm$^{-3}$ s$^{-1}$, which is two orders of magnitude less than the external mass transfer rate, indicating that the reaction rate is independent of the external mass transfer effects. It is also seen from the effect of particle sizes below 90 μm, and from the high values of activation energy, that intra-particle diffusional resistance is absent and thus the effectiveness factor in eqn. (1c) and (2) is unity. Thus, the reaction could be controlled by one of the following steps, namely, (a) adsorption (b) surface reaction or (c) desorption. Therefore, further development of the actual reaction mechanism was undertaken.

### Development of mechanistic model

In the case of the present studies, it is essential to understand the reaction mechanism to develop a suitable model. The initial rate data can be analysed on the basis of Langmuir–Hinshelwood–Hougen–Watson (LHHW) or Eley–Rideal mechanisms. For the initial rate data, the following analysis is most appropriate. The mechanism shown in Fig. 1 can be used to arrive at the LHHW type of mechanism.

1. Adsorption of 4-chlorobenzoyl chloride (A) on a vacant site S is given by:

$$\text{A} + \text{S} \overset{K_A}{\rightleftharpoons} \text{AS} \qquad (a)$$

Similarly adsorption of benzene (B) on a vacant site S is represented by:

$$\text{B} + \text{S} \overset{K_B}{\rightleftharpoons} \text{BS} \qquad (b)$$

2. Surface reaction of AS with BS, in the vicinity of the site, leading to formation of 4-chlorobenzophenone (ES) on the site.

$$\text{AS} + \text{BS} \overset{K_2}{\rightleftharpoons} \text{ES} + \text{WS} \qquad (c)$$

Desorption of 4-chlorobenzophenone (ES) and HCl (WS)

$$\text{ES} \overset{1/K_E}{\rightleftharpoons} \text{E} + \text{S} \qquad (d)$$

$$\text{WS} \overset{1/K_W}{\rightleftharpoons} \text{W} + \text{S} \qquad (e)$$

The total concentration of the sites, C$_t$ expressed as,

$$C_t = C_S + C_{AS} + C_{BS} + C_{ES} + C_{WS}$$

or,

$$C_t = C_S + K_AC_AC_S + K_BC_BC_S + K_EC_EC_S + K_WC_WC_S \qquad (5)$$

or, the concentration of vacant sites,

$$C_S = \frac{C_t}{(1 + K_AC_A + K_BC_B + K_EC_E + K_WC_W)} \qquad (6)$$

If surface reaction (c) controls the rate of reaction, then the rate of reaction of A is given by

$$-r_A = \frac{dC_A}{dt} = k_2C_{AS}C_{BS} - k_2'C_{ES}C_{WS} \qquad (7)$$

$$\frac{-dC_A}{dt} = \frac{k_2\{K_AK_BC_AC_B - (K_EK_WC_EC_W)/K_2\}C_t^2}{(1 + K_AC_A + K_BC_B + K_EC_E + K_wC_w)^2} \qquad (8)$$

when the reaction is far away from equilibrium

$$\frac{-\mathrm{d}C_A}{\mathrm{d}t} = \frac{k_2 C_t^2 K_A K_B C_A C_B}{(1+\Sigma K_i C_i)^2} \tag{9}$$

$$= \frac{k_{R2} w C_A C_B}{(1+\mathrm{S}k_i C_i)^2} \tag{10}$$

where

$$k_{R2}w = k_2 C_t^2 K_A K_B \tag{11}$$

and $w$ is catalyst loading.

If the adsorption constants are very small, then the above equation reduces to

$$\frac{-\mathrm{d}C_A}{\mathrm{d}t} = k_{R2} C_A C_B w \tag{12}$$

Let

$$\frac{C_{Bo}}{C_{Ao}} = M, \tag{12a}$$

the molar ratio of benzene to 4-chlorobenzoyl chloride at time $t = 0$. Then eqn. (10) can be written in terms of fractional conversion as

$$\frac{\mathrm{d}X_A}{\mathrm{d}t} = k_{R2} w C_{Ao}(1 - X_A)(M - X_A) \tag{13}$$

which upon integration leads to:

$$\ln\{(M - X_A)/M(1 - X_A)\} = k_{R2} w C_{Ao}(M - 1)t \tag{14}$$

when $M$ is other than unity.

For equimolar quantities of A and B, the integration of eqn. (10) yields eqn. (15):

$$X_A/(1 - X_A) = C_{Ao} k_{R2} w t \tag{15}$$

To validate the above mechanism, plots were made in consonance with eqn. (12) and (13), as shown in Fig. 8 and 9, respectively.

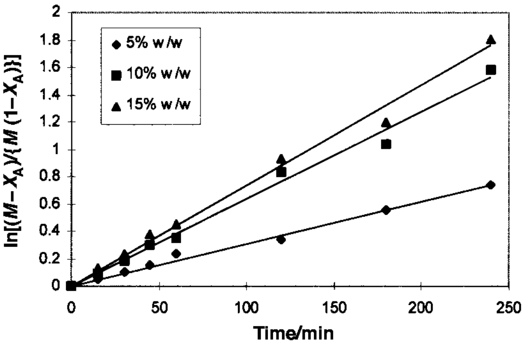


**Fig. 8** Plot of $\ln[(M - X_A)/\{M(1 - X_A)\}]$ *vs.* time (benzene: 4-chlorobenzoyl chloride = 10:1, speed of agitation = 800 rpm, catalyst = S-ZrO$_2$, $T$ = 70 °C).

Fig. 8 shows three straight lines passing through the origin at catalyst loadings of 5, 10 and 15% w/w respectively. The slopes of these lines are $k_1 = k_{R2} w C_{Ao}(M - 1)$ which are functions of $w$ for the same molar ratio $M$. Thus, plots of $k_1$ were made against $w$ to show that it is a linear relationships (Fig. 10). The slope gives the value of $k_{R2}$ as cm$^6$ gmol$^{-1}$ g$^{-1}$ s$^{-1}$.

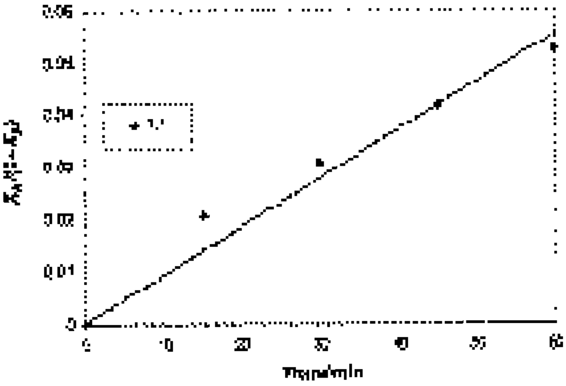


**Fig. 9** Plot of $X_A/(1 - X_A)$ *vs.* time for 1:1 mole ratio.

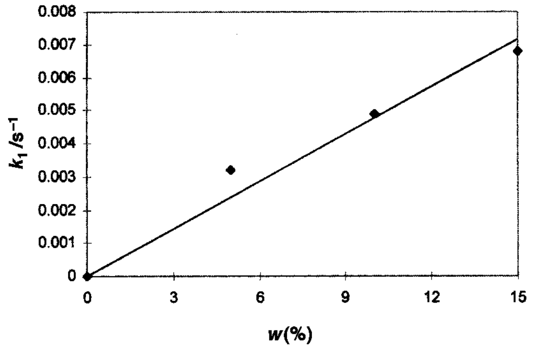


**Fig. 10** Plot of slope ($k_1$) *vs.* catalyst loading.

For equimolar quantities of the reactants, eqn. (13) is valid as shown in Fig. 9. It would therefore mean that the reaction mechanism is of LHHW type with a very weak adsorption of both the reactants in the absence of any diffusional resistance.

The values of $k_1$ were also found at different temperatures at the same value of $w$ and $M$. The Arrhenium plot of ln $k_1$ *vs.* $T^{-1}$ is shown in Fig. 11 from which the activation energy was calculated as 8.8 kcal mol$^{-1}$. The high value of activation energy also supported the fact that the overall rate of reaction is not influenced by either external mass transfer or intraparticle diffusion resistance and it is an intrinsically kinetically controlled reaction on active sites.

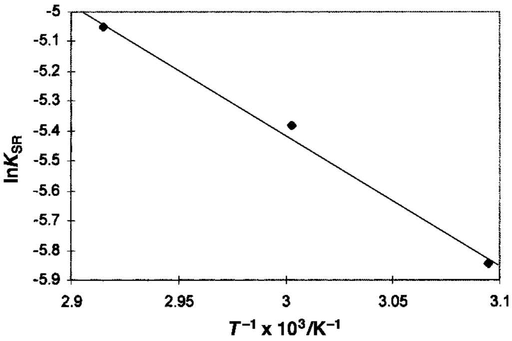


**Fig. 11** Arrhenius plot.

## Reusability of the catalyst

The catalyst reusability was studied three times, including the use of fresh catalyst (Fig. 12). The catalyst was filtered and reused in the next batch without any treatment. Since amount of catalyst used was only 1.98 g in a typical batch, there are inevitably losses of particles

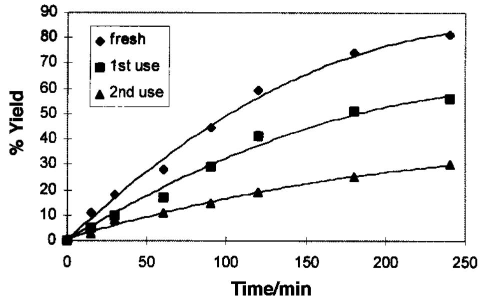


**Fig. 12** Effect of reusability of catalyst (benzene:4-chlorobenzoyl chloride = 10:1, speed of agitation = 800 rpm, catalyst = S-$ZrO_2$, catalyst loading = 10% w/w).

during filtration. The actual amount used in the next batch is almost 20% less than the previous batch and thus the loss in yield on subsequent use is mainly due to the smaller quantity of catalyst used. By accounting for this loss, the initial rates drop by about 10% in the subsequent run. On a larger scale perhaps a better idea of catalyst reusability will be evident.

## Conclusion

This work has addressed an important problem related to green chemistry wherein the highly polluting Friedel–Crafts catalyst $AlCl_3$ can be replaced by an environmentally benign catalyst. The acylation of benzene with 4-chlorobenzoyl chloride was studied systematically over sulfated zirconia, which was found to be the only effective catalyst among several others. The acylation reaction is 100% selective towards 4-chlorobenzophenone. The kinetics of the reaction was studied to establish that the reaction obeys the Langmuir–Hinshelwood–Hougen–Watson mechanism with a very weak adsorption of the reactants. The reaction is intrinsically kinetically controlled.

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## References

1 G. A. Olah, *Friedel–Crafts and Related Reactions*, Wiley-Interscience, New York, 1963, vol. 1.
2 J. A. Hyat and P. W. Raynolds, *J. Org. Chem.*, 1984, **49**, 384.
3 P. Sommai, O. Kazumi, M. Masahiro, M. Satoni and N. Masakatsu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1703.
4 P. S. Kumbhar and G. D. Yadav, *Chem. Eng. Sci*., 1989, **44**, 2535.
5 T. S. Thorat, V. M. Yadav and G. D. Yadav, *Appl. Catal. A: Gen*., 1992, **90**, 73.
6 G. D. Yadav, P. S. Kumbhar and T. S. Thorat, *Tetrahedron Lett*. 1993, **34**, 529.
7 G. D. Yadav and P. H. Mehta, *Ind. Eng. Chem. Res.*, 1994, **33**, 2198.
8 G. D. Yadav, *PAFAI J.*, 1994, **16**, 13.
9 G. D. Yadav and N. Kirthivasan, *J. Chem. Soc., Chem. Commun.*, 1995, 203.
10 A. B. Dixit and G. D. Yadav, *React. Funct. Polym.*, 1996, **31**, 237.
11 A. B. Dixit and G. D. Yadav, *React. Funct. Polym.*, 1996, **31**, 251
12 G. D. Yadav and T. S. Thorat, *Tetrahedron Lett*., 1996, **37**, 5405.
13 G. D. Yadav and T. S. Thorat, *Ind. Eng. Chem. Res.*, 1996, **35**, 721.
14 G. D. Yadav and V. V. Bokade, *Appl. Catal. A: Gen.*, 1996, **147**, 299.
15 G. D. Yadav and V. V. Bokade, *Appl. Catal. A: Gen.*, 1997, **154**, 29.
16 G. D. Yadav and D. V. Satoskar, *J. Chem. Technol. Biotechnol.*, 1997, **69**, 438.
17 G. D. Yadav and M. S. Krishnan, *Org. Process Res. Dev.*, 1998, **2**, 95.
18 G. D. Yadav and M. S. Krishnan, *Ind. Eng. Chem. Res.*, 1998, **37**, 3358.
19 G. D. Yadav and J. J. Nair, *Chem. Commun*., 1998, 2370.
20 G. D. Yadav and M. S. Krishnan, *Chem. Eng. Sci.* 1999, in press.
21 M. Labrouiller, C. le Roux, H. Gaspard, A. Laporterie and J. Dubac, *Tetrahedron Lett.*, 1997, **38**, 8871.
22 N. R. Ayyanger, R. J. Lahoti and K. Srinivasan, *Synthesis*, 1991, **4**, 322.
23 X. Song and A. Sayari, *Catal. Rev. Sci. Eng.*, 1996, **38**, 329.
24 G. D. Yada and J. J. Nair, *Microporous Mesoporous Mater. (fromerly Zeolites)*, 1999, in press.
25 P. S. Kumbhar, V. M. Yadav and G. D. Yadav, in *Chemically Modified Oxide Surfaces*, ed. D. E. Layden and W. Collins, Gordon and Breach, New York, 1989.

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# Selective production of 1-arylalkenes

## Synthesis of 1-aryl-2-alkenes and 1-arylalkanes *via* Friedel–Crafts alkylation of aromatic substrates with allylic alcohols over solid acid catalysts

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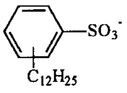
### Summary

Moderately activated benzenoid compounds undergo alkylation with allylic chlorides and particularly allylic alcohols over solid acid catalysts. Acidic K10 clay is the optimal catalyst and allows almost exclusive attack at the terminal position of the intermediate allyl cation to yield 1-aryl-2-alkenes. Catalytic hydrogenation quantitatively yields the corresponding 1-arylalkanes. Phenol also reacts readily but gives a significant quantity (*ca.* 12%) of 3-aryl-1-butene along with 1-aryl-2-butene.

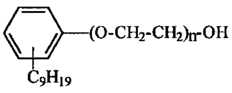
### Introduction

The last few decades have seen a dramatic increase in the production of synthetic surface active agents (surfactants)[1] and lubricating oils.[2] Unfortunately, the methods of production of these materials suffer from the twin disadvantages that they involve use of environmentally undesirable catalysts such as aluminium chloride or hydrogen fluoride and that the products obtained are usually not the most desirable isomers in terms of their physical properties and/or their biodegradability. Therefore, there is a strong need for new procedures that can overcome these difficulties and lead to benefits in terms of cleaner technology. We now report the selective production of 1-arylalkenes from aromatic substrates and allylic alcohols under the influence of an acidic clay, reactions that provide substantial benefits of the kind required.

Surfactants owe their properties to their characteristic hydrophilic–hydrophobic structure, which enables them to aggregate at the surface of an aqueous solution and hence reduce its surface tension properties. Arylalkane-derived surfactants such as alkylbenzenesulfonates **1** and to a lesser extent alkylphenol ethoxylates **2** are important raw materials for the formulation of many detergents.



**1**



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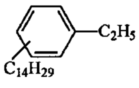

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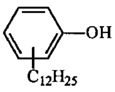

**4**

Alkylbenzenesulfonates are typically produced by Friedel–Crafts alkylation of benzene using $AlCl_3$ or HF as catalysts followed by sulfonation with oleum or free sulfur trioxide. These surfactants are chemically stable and have excellent cleaning properties. The hydrophilic sulfonate group is negatively charged in aqueous solution whilst the hydrophobic carbon chain typically has 10–14 carbon atoms because the surface activity is not sufficient with alkyl groups containing less than 6 carbon atoms and the solubility in water is too low with more than 15 carbon atoms. The carbon chain may be linear or branched but it has been found that isomers with linear alkyl groups are more viscous and more easily biodegradable than analogous branched isomers and that among linear isomers 1-arylalkanes[1] are better than 2- or 3-arylalkanes.

Dialkylbenzenes containing one short (2–4 carbon atoms) and one long (14–18 carbon atoms) linear alkyl group **3** are used as synthetic lubricating oils or additives.[2] Dodecylphenols **4** in derivatized form are also commercially important as additives for lubricants,[3] but whilst branched chain isomers are still being produced in large quantities from propylene tetramer with ion exchange resins, linear isomers are now of growing interest because of their higher viscosity indices.

## Green Context

**Alkylbenzenesulfonates are manufactured on a very large scale as intermediates in the synthesis of surfactants. These materials are prepared by Friedel–Crafts alkylation of benzene with alkenes, and typically a range of isomers is produced. Attachment of the arene as close as possible to the terminus of the aliphatic chain is preferred because of better biodegradability. The linear 1-aryl compound would be ideal, but is not formed in the traditional process. The use of allylic alcohols is shown to give the 1-aryl compound with excellent selectivity after hydrogenation of the arylalkene formed directly in a solid acid catalysed process.** ***DJM***

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† Formerly known as the University College of Swansea

Since 1-arylalkanes are potentially best for the detergent and lubricant industries it is unfortunate that they are not usually available *via* direct Friedel–Crafts alkylation of aromatic substrates[4] on account of the tendency of the primary carbocation intermediates to rearrange. Consequently, when they are needed in pure form they are generally prepared by Friedel–Crafts acylation followed by reduction of the ketone so produced to the hydrocarbon level. These procedures, however, are too costly and too unfriendly towards the environment to be used for production of the bulk requirements of the detergents or lubricants industries, which therefore continue to use mixtures consisting mainly of 2-arylalkanes.

There is considerable interest nowadays in the use of solid catalysts such as zeolites, clays and silica–aluminas to control organic reactions.[5–8] Grey has produced 2-tolylalkanes in a highly selective manner by reacting toluene with alkenes over a H-mordenite zeolite.[9] In accord with our own continuing interest in the use of solids for controlled organic synthesis,[7,10,11] we decided to investigate the possibility of using a solid acid to catalyse production of 1-arylalkanes *via* Friedel–Crafts alkylation. We now report the successful use of allylic alcohols in the selective production of 1-aryl-2-alkenes over solid acid catalysts.[12] The 1-aryl-2-alkenes are easily hydrogenated to give 1-arylalkanes.

## Results and discussion

Our initial investigations centred around the alkylation of toluene because this substrate enabled us to study both the proportions of 1-tolylalkanes produced and any possible change in ring isomer distribution. Unfortunately, zeolite catalysed reactions with conventional alkylating agents met with only limited success.

We first modified the conditions used by Grey[9] in attempts to divert the reaction to produce 1-arylalkanes. A wide range of reaction temperatures was monitored using 1-hexene as the test reagent and H-mordenite as the catalyst. Temperatures of around 110 °C produced predominantly 2-(*p*-tolyl)hexane whilst higher temperatures (*ca*. 160 °C) or longer reaction times produced predominantly 3-tolylhexanes *via* side chain rearrangement either intramolecularly or intermolecularly. Significantly, however, 1-tolylhexanes were not formed and further studies showed that there was no advantage in using solvents other than the aromatic substrate itself; nor was there any marked improvement when using cation exchanged mordenites or dealuminated H-mordenite. This prompted us to turn our attention to the use of 1-halogenoalkanes as alkylating agents in the hope that the product might be formed without rearrangement.

Friedel–Crafts alkylations with primary alkyl halides using conventional catalysts such as $AlCl_3$ or $AlBr_3$ produce a mixture of primary and secondary alkylbenzenes.[13] Since rearrangements accompanying these reactions are very dependent upon reaction conditions, we hoped to be able to control them by use of zeolites to produce 1-arylalkanes selectively. Toluene was successfully alkylated using 1-hexyl halides over H-mordenite, but the proportions of 1-tolylhexanes never exceeded 22% (I<Br<Cl). A maximum of 32% was achieved using strongly acidic dealuminated HY zeolite. Other primary alkyl halides gave even lower proportions. Resins, clays and amorphous aluminosilicates were used instead of zeolites but yields were always poor and the proportions of 1-tolylhexanes never exceeded 19%.

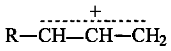
We next turned our attention to allylic derivatives of types **5** and **6** in the hope that these would generate the stabilised allylic cation **7** and that this would react preferentially at its terminal position with aromatic substrates to give allylarenes **8**.

$R{-}CH{=}CH{-}CH_2X$

**5** (*E*)

$R{-}C(X)H{-}CH{=}CH_2$

**6**



$R{-}\overset{+}{CH{-}CH{-}CH_2}$

**7**

$R{-}CH{=}CHCH_2Ar$

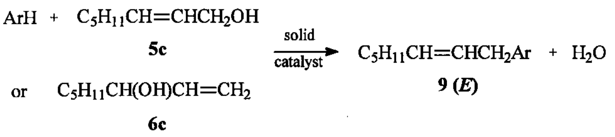
**8**

Apart from simple allylation (R = H)[4a,b] little work has been reported using allylic reagents of this type. Although these reactions are usually much faster than the analogous ones with primary alkyl halides or alcohols, they generally produce complex mixtures. As a general rule, in homogeneous alkylations with allylic halides protonic acids tend to catalyse reactions at the double bond while Lewis acids tend to catalyse allylic substitution.[4b]

In the presence of H-mordenite, allylic chlorides **5a** and **6a** (R = Me, X = Cl) reacted with refluxing toluene to give reasonable yields of the terminally substituted product **8a** (R = Me, Ar = tolyl) with a typical *o*/*p* ratio of 52/48. There was little evidence of further allylation or of addition of hydrogen chloride to the double bond as reported for homogeneous conditions.[14] The reaction was also applied successfully to (*E*)-1-chloro-2-octene (**5b**, R = pentyl, X = Cl) with similar results. Cation exchanged mordenites did not significantly improve the *para*-selectivity.

Although allylic chlorides produced satisfactory yields they showed significant drawbacks. In particular, hydrogen chloride is not a favourable by-product since it is corrosive, can damage the structure of the solid catalyst and can act as a competitive catalyst in its own right, leading perhaps to a different selection of products. Therefore, allylic alcohols were studied more extensively and **5c** and **6c** (R = pentyl, X = OH) were chosen as the test reagents. 1-Octen-3-ol **6c** was found to be a little less reactive than (*E*)-2-octen-1-ol **5c**. However, **6c** has the advantage of being much cheaper.

The effectiveness of a number of different catalysts was tested under a standard set of reaction conditions (Scheme 1). The results are shown in Table 1.



**Scheme 1**

Several important features emerge from Table 1. (i) There is little or no reaction under these conditions in the absence of a catalyst or with a soluble acid catalyst ($MeSO_3H$). (ii) Several catalysts, notably silica, Amberlyst 15, H-ZSM-5 and H-X, bring about decomposition of the octenol without causing alkylation. The most likely explanation for this was thought to be dehydration of the alcohol to form conjugated dienes, and the occurrence of such products was confirmed by GC-MS analysis of a product mixture. (iii) The reaction was successfully catalysed by H-mordenite and H-Y, both of which have large pores. There was no improvement in product yields under milder conditions, suggesting that the rate of dehydration is similar to that of allylation. There was no evidence of polyalkylation as the reason for poor material balances and adsorption of the alcohol could be dismissed as the material balance remained constant when smaller amounts of catalyst were used. (iv) Of the catalysts tried, the acidic clay K10 was the most effective catalyst for the reaction.

In the case of the zeolite catalysts, in particular H-Y with a silica:alumina ratio of 40:1, a further set of peaks was prominent in

**Table 1** Effects of different catalysts in the reaction depicted in Scheme 1 (ArH = toluene)[a]

| Catalyst | Reagent | Octenol converted (%)[b] | Yield of **9**[c,d] | Ratio *o*:*m*:*p* |
|---|---|---|---|---|
| None | **6c** | 9 | 0 | — |
| $MeSO_3H$ | **6c** | 2 | 0 | — |
| Amberlyst-15 | **6c** | 54 | 0 | — |
| Silica | **6c** | 17 | 0 | — |
| Synclyst (silica–alumina) | **6c** | 97 | 62 | 49:5:46 |
| K10 | **6c** | 100 | 79 | 47:6:47 |
| K10 | **5c** | 100 | 89 | 48:5:47 |
| H-ZSM-5 | **6c** | 48 | 0 | — |
| H-Mordenite | **6c** | 100 | 61 | 45:6:49 |
| H-Mordenite | **5c** | 100 | 69 | 44:8:48 |
| H-X ($SiO_2$:$Al_2O_3$ = 2.5:1) | **6c** | 35 | 0 | — |
| H-Y ($SiO_2$:$Al_2O_3$ = 5:1) | **6c** | 100 | 71 | 39:14:47 |
| H-Y ($SiO_2$:$Al_2O_3$ = 5:1) | **5c** | 100 | 83 | 49:6:45 |
| H-Y ($SiO_2$:$Al_2O_3$ = 40:1) | **6c** | 100 | 33 | — |

[a] Under standard conditions using catalyst (96 mg) in toluene (7.5 $cm^3$) at reflux and addition of octenol (320 mg, 2.5 mmol) in toluene (5 $cm^3$) over a few min with stirring, followed by a further 5 min at reflux. [b] Determined by amount of octenol remaining (by GC). [c] Determined by GC using an added standard. [d] Products obtained following isolation by spinning band distillation of larger scale reaction mixtures were characterized by NMR and mass spectrometry and by conversion into identifiable arylalkanes by catalytic hydrogenation.

the GC of the product mixture. An increase in the proportions of these products occurred with longer reaction times. The mass spectral fragmentation patterns (by GC-MS) of the new products, and their stability towards hydrogenation, suggested very strongly that they were cyclised products.

Since the acidic clay K10 was the most effective catalyst tried, acidic clays were chosen for further investigation. The use of acidic clays in Friedel–Crafts alkylations has been reported before, but benzylic alcohols were the only unsaturated alcohols investigated.[5] We decided to study the effectiveness of a range of clay catalysts for the alkylation of toluene using **6c**. The reactions were followed by gas chromatography and the yield of **9** obtained was monitored. Various acid-activated clays, mostly commercial, obtained by treatment with acids such as HCl, $H_2SO_4$ and $H_3PO_4$, along with natural clays such as Texas montmorillonite and bentonite, were dried at 110 °C overnight and their activities were then compared. The results are shown in Fig. 1.

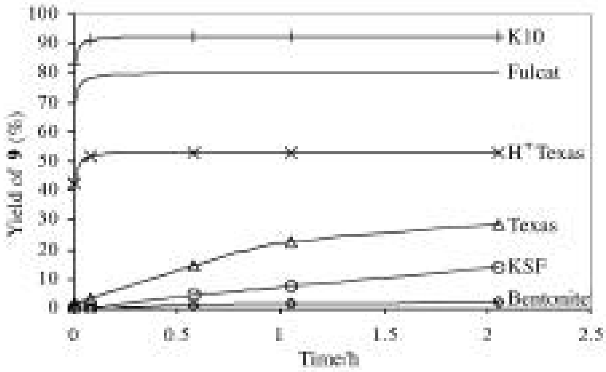


**Fig. 1** Alkylation of toluene with 1-octen-3-ol **6c** over acid-activated clays (*e.g.* 0.096 g K10; 0.320 g, 2.5 mmol octenol; 7.5 ml toluene, 110 °C; for details of clays see Experimental section).

Untreated clays exhibited little or no activity. In contrast, acid-activated clays (except $H^+$ Texas and KSF) were very successful catalysts (*ca.* 74–92% yield). It is known that strong treatment with acid leads to partial destruction of clay structures and consequently higher surface areas, whereas mild treatments (as for $H^+$ Texas) result almost exclusively in simple proton exchange within the interlayer. The yields for the reactions over acid treated clays were therefore plotted against the surface areas of the catalysts (Fig. 2). A good correlation was observed, indicating that increased surface area, rather than increased acid strength, is the factor having most effect on the activity of the catalysts.

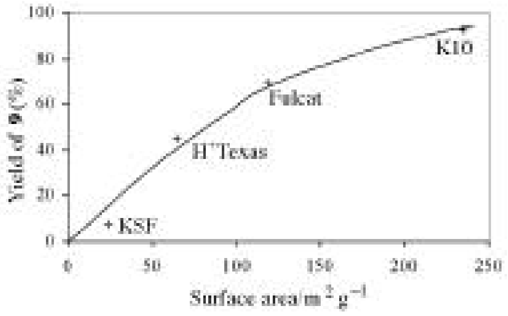


**Fig. 2** Correlation between yield of **9** (after 15 min) and surface area of the catalyst (conditions as for Fig. 1).

In order to test the influence of the interlamellar cations, various cation-exchanged clays were prepared from Texas montmorillonite following a standard procedure.[15] Multivalent cations such as $Al^{3+}$, $Cr^{3+}$, $La^{3+}$ and $Fe^{3+}$ were chosen because they polarize interlamellar water molecules and therefore generate some acidity. The activities of the various clays were then compared (Fig. 3).

As shown in Fig. 3, the yield of **9** was improved substantially (to *ca.* 40–60%) by use of the cation-exchanged clays instead of the natural clay. The aluminium-exchanged clay even gave a somewhat better yield than the proton-exchanged analogue. However, even the most active cation-exchanged clays were not as active as the clays which have been more forcibly treated with acid, such as K10. Therefore, K10 was chosen for further investigation. We next conducted a series of experiments to determine the effect of the alcohol : catalyst ratio on the reaction and the results are shown in Fig. 4. Experiments were conducted with a sample of zeolite HY for comparison and with both hydrated (as purchased) and dried (110 °C) samples of K10.

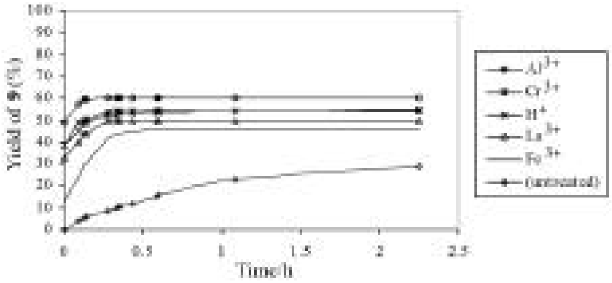


**Fig. 3** Alkylation of toluene with 1-octen-3-ol **6c** over different cation-exchanged Texas montmorillonite clays (conditions as for Fig. 1).

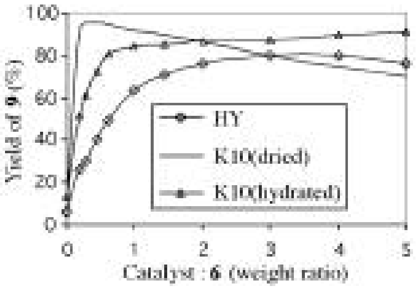


**Fig. 4** Alkylation of toluene with **6c** over K10 or HY ($SiO_2$:$Al_2O_3$ = 4.74:1) at reflux for 5 min.

As shown in Fig. 4, K10 was more active than HY and more active in its dried form. However, with large amounts of catalysts there was little difference between them and all gave high yields of **9**. Water is generated by the reaction, and a Dean–Stark apparatus was therefore used to remove the water as it was formed. With smaller amounts of catalyst the situation should soon be reached whereby the hydrated and dried forms would behave similarly. The greater initial activity of the dried K10 presumably reflects both the higher intrinsic activity of the dried K10 and the longer time to reach equilibrium water content with the hydrated form.

Small amounts of K10 (mass ratio of octenol : catalyst of *ca.* 1:0.3) catalyse the reaction very successfully and there is little value in use of larger quantities. In an attempt to find suitable conditions for use of even lower amounts, the reaction progress was studied as a function of time with just 5% (weight per unit weight octenol used) of K10. With this small amount of catalyst the reaction required a longer time but still achieved a yield of around 80% after about 30 minutes. Interestingly, the yield did not increase further thereafter even though some octenol remained until 3 h.

Since the amount of interlamellar water present in the initial catalyst appeared to be a critical parameter, treatment of K10 before use at several temperatures was investigated. Attempts to dry the K10 by heating at 60 °C under vacuum or at 200 °C at atmospheric pressure were not beneficial. Presumably drying was not effective under the former conditions while partial collapse of the lamellar structure took place under the latter conditions. Optimum reactivity was achieved after drying in an oven at 110 °C. The K10 was also found to retain about 50% of its activity after being used and regenerated (at 110 °C) three times.

Finally, a reaction was carried out using zinc chloride supported on K10.[16] This showed that the latter was not as active as K10 alone for catalysis of this reaction.

In order to gauge the generality of the process for this reaction, K10 in quite high ratio was applied to the reactions of a range of aromatic substrates with **6c**. The results are given in Table 2.

It is likely that the optimal catalyst would be different for different substrates, with more acidic catalysts giving better results for deactivated substrates and less acidic ones giving better results for activated substrates in accord with the comments relating to Table 1. However, it is clear from the results in Table 2 that K10 can lead to good yields of 1-aryl-2-alkenes from a range of substrates of moderate activity.

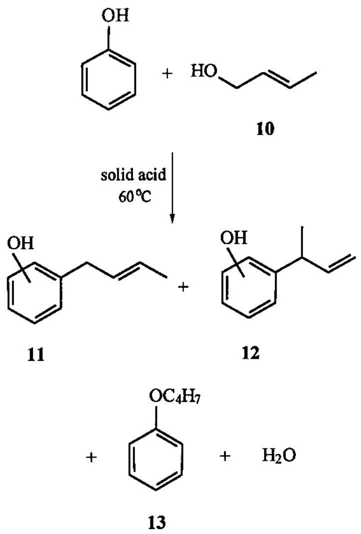
**Table 2** Syntheses of products **9** according to Scheme 1 with K10 as catalyst[a]

| Ar | Reaction temp./°C | Yield of **9** (%)[b] | Ratio *o*:*m*:*p*[c] |
|---|---|---|---|
| Ph | 80 | 78 | — |
| $MeC_6H_4$ | 111 | 92 | 46:5:49 |
| $EtC_6H_4$ | 111 | 77 | 42:4:54 |
| $Pr^iC_6H_4$ | 111 | 68 | 36:0:64 |
| $Bu^tC_6H_4$ | 111 | 78 | 24:0:76 |
| $FC_6H_4$ | 85 | 43 | 16:0:84 |
| $MeOC_6H_4$ | 111 | 72[d] | 55:0:45 |

[a] Ratio alcohol : catalyst = 1:2; reaction time 5 min for each case. [b] Isolated yield following distillation. [c] Determined by GC. [d] The K10 was not dried prior to use in this case.

Alkylbenzenes were alkylated with **6c** in high yields to form **9** almost exclusively. The alkylation of fluorobenzene also produced **9** selectively, but the yield was poor because **6c** suffered high levels of decomposition into dienes and ethers in the polar environment. Polar solvents tend to favour elimination rather than substitution reactions and they also have a greater tendency to swell clays. In contrast, when the activated compound anisole was alkylated, a high yield was achieved, although a significant amount of 3-aryl-1-octene was also formed in this case. This is presumably because the more active ring is less discriminating in its reaction with the allylic cation.

In view of the importance of alkylphenol ethoxylates **2** in the surfactant industry, attention was next turned to the alkylation of phenols. The reaction of phenol with crotyl alcohol (**10**) was chosen as the control reaction (Scheme 2).



**Scheme 2**

Typically, an excess of phenol was added to **10** and the mixture was heated gently to 60 °C before addition of the catalyst.

**Table 3** Alkylation of phenol with butenol **10** over different catalysts[a]

| Catalyst | Conversion of **10** (%) | Total yield (%) | Isomer distribution (%) | | | | |
|---|---|---|---|---|---|---|---|
| | | | **11** | *o*:*p* | **12** | *o*:*p* | **13** |
| $H_3PO_4$[b] | 100 | 62 | 78 | 54:46 | 15 | 40:60 | 7 |
| $H_3PO_4$[b,c] | 100 | 49 | 87 | 53:47 | 13 | 46:54 | 0 |
| K10 (dried) | 100 | 93 | 87 | 51:49 | 13 | 54:46 | 0 |
| $Al_2O_3$–$SiO_2$[d] | 73 | 56 | 82 | 48:52 | 11 | 45:55 | 7 |
| HY | 68 | 69 | 80 | 49:51 | 14 | 43:57 | 6 |
| HM | 50 | 33 | 82 | 41:59 | 12 | 42:58 | 6 |
| None | 0 | 0 | — | — | — | — | — |

[a] 60 °C for 1h; catalyst : **10** = 1.4:1 (weight ratio). [b] 1 molar equivalent (based on **10**). [c] 60° C for 20 h. [d] 13% $Al_2O_3$ (by weight).

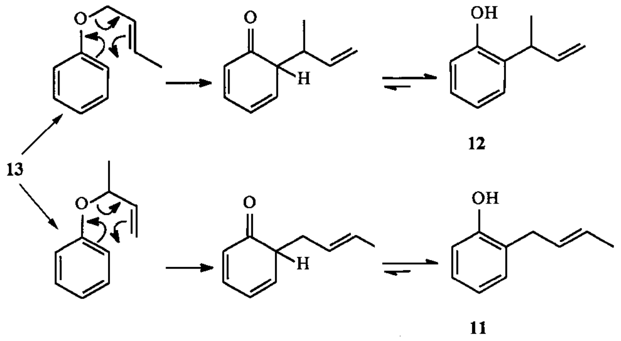
**Table 4** Alkylation of phenol with butenol **10** over dried K10 under mild conditions

| K10:**10** (weight) | Temp./°C | Time/h | Conversion of **10** (%) | Total yield (%) | Isomer distribution (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **11** | *o*:*p* | **12** | *o*:*p* | **13** |
| 2.78 | 60 | 1 | 100 | 97 | 88 | 50:50 | 12 | 50:50 | 0 |
| 1.39 | 60 | 1 | 100 | 93 | 87 | 51:49 | 13 | 54:46 | 0 |
| 0.28 | 60 | 1 | 89 | 80 | 85 | 51:49 | 11 | 45:55 | 4 |
| 0.06 | 60 | 1 | 27 | 24 | 78 | 49:51 | 9 | 33:67 | 13 |
| 1.39 | 20 | 1 | 20 | — | 70 | 49:51 | 12 | 50:50 | 18 |
| 1.39 | 20 | 7 | 66 | — | 81 | 49:51 | 9 | 56:44 | 10 |
| 1.39 | 20 | 23 | 79 | 68 | 87 | 49:51 | 9 | 44:56 | 4 |

The reported reaction of phenol with allylic alcohols[17–19] was repeated to provide a baseline for comparison, but the *para*-selectivity claimed was found to be incorrect, presumably because the early research suffered from a lack of sophisticated analytical instrumentation. Both *ortho* and *para* isomers of the main product **11** were formed, in roughly equal proportions, along with a substantial amount of **12** and a small amount of phenyl butenyl ether, **13**. The reaction was therefore performed with a range of catalysts, with the results shown in Table 3.

The reaction profile using solid acid catalysts was not substantially different from that with phosphoric acid as catalyst but the procedure was simpler, with less catalyst required, easier work-up and higher yields. K10 and HY were again found to be the most successful catalysts.

The successful reaction over dried K10 was carried out with different amounts of catalyst at 60 °C and at room temperature, in order to determine any changes in product distribution (see Table 4). Phenyl butenyl ethers were formed in substantial amounts at room temperature, or at the higher temperature when the amount of catalyst was small. This suggests that O-alkylation either takes place only when the rate of C-alkylation is low or that phenyl butenyl ethers are formed initially but then undergo a Claisen rearrangement as shown in Scheme 3.



**Scheme 3**

In order to test these possibilities, phenyl butenyl ether **13** was isolated by fractional distillation of the product from an alkylation of phenol with butenol **10** conducted on a large scale at room temperature. It was characterized by $^1H$ NMR and $^{13}C$ NMR spectroscopy and mass spectral analysis. We were then able to show that when a solution of **13** in dichloromethane was treated with K10, *ortho* and *para* isomers of **11** and **12** were formed. This result suggests that phenyl butenyl ethers are formed first and then undergo a Claisen rearrangement when phenol is alkylated with **10** over solid catalysts. Further rearrangements of the intermediate cyclohexadienones are also possible.

The substantial amounts of (*E*)-3-aryl-1-butenes **12** formed were believed to result from the high reactivity of phenol. Several *para*-monosubstituted and *ortho*-disubstituted phenols (having Cl, Me or *t*-Bu groups) were alkylated under the same conditions and the proportions of the 3-aryl-1-butenes **12** formed ranged from 9% to 45%. It is therefore clear that reactive aromatic substrates show a greater tendency to react at the 3-position of the allyl group than non-activated substrates, which is not surprising.

With a successful procedure for the synthesis of 1-aryl-2-alkenes **9** in hand, it was necessary only to convert them into the corresponding 1-arylalkanes by hydrogenation according to Scheme 4.[20] This was straightforward and quantitative. Thus, the two step sequence represented by Schemes 1 and 4 provides a new, high yielding and convenient route to 1-arylalkanes **14**.

$$C_5H_{11}CH{=}CHCH_2Ar \xrightarrow[\text{Pd/C cat.}]{H_2} C_5H_{11}CH_2CH_2CH_2Ar$$

**9** (*E*) **14**

**Scheme 4**

We also note that solids which generally exhibit Brønsted acidity act to produce allylic substitution rather than addition to the double bond, in contrast to the reported situation with soluble acids.[4b]

## Conclusion

Linear 2-arylalkanes may be produced selectively in high yields by Friedel–Crafts alkylation with 1-alkenes over a mordenite zeolite. Linear 1-arylalkanes can be produced selectively in high yields by a two step sequence involving as the first step Friedel–Crafts allylation with allylic alcohols over a solid acid catalyst, the most active being K10 clay, followed by hydrogenation.

Depending on the solid acid catalyst used and the reaction conditions the reaction with allylic alcohols may be accompanied by dehydration of the starting alcohol and/or by further cyclisation of the 1-arylalkenes formed. For activated substrates, 3-aryl-1-alkenes may be produced in significant amounts alongside the 1-aryl-2-alkenes. The new allylation process should prove to be of considerable significance for synthesis of alkylaromatic compounds.

## Experimental

All reactants were of high commercial grade and except where stated were used without further purification. As water is adsorbed readily by the catalysts used, the aromatic substrate (also employed as solvent) was dried prior to use. Thus, toluene was stirred over $CaCl_2$, filtered, distilled over phosphorus pentoxide under nitrogen and stored over 4A molecular sieves.

All reactions were analysed by gas chromatography (GC) using an internal standard. Calibration procedures often required initial isolation of the products, usually as a mixture of isomers. Toluene alkylations were monitored on a Phillips PU 4400 model with a FID detector using a methyl silicone gum HP1 (10 m × 0.5 mm) column with He as the carrier gas. Alkylation of phenols and hydrogenations were monitored using a Carbowax (30 m × 0.32 mm) column with He as the carrier gas.

All solid catalysts used, apart from clays, were calcined at 550 °C overnight before use. Unless otherwise stated, clays were dried in an oven at 110 °C overnight. Modified zeolites or clays (proton-exchanged, cation-exchanged, impregnated) were all prepared following standard procedures.[21]

### General alkylation procedures

All alkylation reactions were carried out in a similar fashion. Typical procedures are described below.

#### *Alkylation of toluene with 1-alkenes*

A dry, 25 ml, two-necked, round-bottomed flask equipped with a magnetic follower was charged with the catalyst (*e.g.* H-Mordenite ($SiO_2$:$Al_2O_3$ = 21.1:1)) (0.333 g) and hexadecane (0.200 g, 0.88 mmol). The flask was fitted with a reflux condenser and bubbler and flushed with nitrogen. Toluene (10 ml, 96 mmol) was added and the mixture was brought to reflux. 1-Hexene (1.50 ml, 1.00 g, 12 mmol) was added dropwise over several minutes. Samples were removed periodically, filtered through a sintered glass tube and analysed by capillary column chromatography using a non-polar column.

#### *Alkylation of toluene with primary alkyl halides or alcohols*

A dry, 25 ml, round-bottomed flask equipped with a magnetic follower was charged with the catalyst (*e.g.* H-Mordenite ($SiO_2$:$Al_2O_3$ = 21.1:1)) (0.500 g). A solution of hexadecane (0.250 g, 1.1 mmol) and 1-chlorohexane (0.603 g, 5.0 mmol) in toluene (10 ml) was added. The flask was fitted with a reflux condenser equipped with a $CaCl_2$ tube and the reaction mixture was brought to reflux. Samples were removed periodically, filtered through a sintered glass funnel and analysed by megabore column gas chromatography.

#### *Alkylation of toluene with allylic chlorides*

The procedure was similar to that described for 1-alkenes.

#### *Allylation of toluene with allylic alcohols*

A dry, 25 ml, round-bottomed flask equipped with a magnetic follower was charged with the catalyst (*e.g.* dried K10, 0.096 g). Toluene (7.5 ml) was added, a reflux condenser was fitted and the mixture was brought to reflux. A solution of 1-octen-3-ol (0.320 g, 2.5 mmol) and hexadecane (0.125 g, 0.55 mmol) in toluene (5 ml) was added dropwise into the mixture over several minutes. Samples were removed periodically, filtered through a sintered glass tube and analysed by capillary column gas chromatography.

#### *Allylation of phenols with allylic alcohols*

A dry, 25 ml, round-bottomed flask was flushed with nitrogen and charged with crotyl alcohol (0.361 g, 5.0 mmol), octadecane (0.213 g, 0.84 mmol, internal standard) and phenol (5 g). The mixture was melted carefully at 60 °C and the catalyst (*e.g.* dried K10, 0.500 g) and a magnetic follower were added. A reflux condenser was fitted and the reaction mixture was refluxed with stirring. Samples were removed periodically and the catalyst was filtered off and washed with dichloromethane. Capillary GC analysis of the filtrate/washings indicated the extent of conversion of the alcohol and the product distribution.

#### *Hydrogenation of 1-aryl-2-alkenes*

A general purpose atmospheric pressure hydrogenation apparatus was used.[20] 1-Aryl-2-alkenes were either used directly in the aryl-H solvent used for their preparation or dissolved in dichloromethane if they had been isolated. The presence of an internal standard in the reaction mixture did not have any effect on the reaction. A sample of Pd/C catalyst (100 mg/mmol of substrate, 5% Pd, 0.046 mmol of Pd) was added and the suspension was shaken with hydrogen at 1 atmosphere ($10^5$ Pa) for 1 h. The mixture was filtered through Celite and analysed by capillary column gas chromatography.

## Acknowledgements

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## References

1 A. Davidsohn and B. M. Milwidsky, *Synthetic Detergents*, Wiley, New York, 1978.
2 H. A. Bouncer, Eur. Patent 160145, 1985; *Chem. Abstr.*, 1986, **104**, 148457r.
3 H. G. Franck and J. W. Stadehofer, *Industrial Aromatic Chemistry*, Springer, Berlin, 1987.
4 (*a*) G. A. Olah, *Friedel–Crafts Chemistry*, Wiley, New York, 1973; (*b*) R. M. Roberts and A. A. Khalaf, *Friedel–Crafts Alkylation*, Marcel Dekker, New York, 1984; (*c*) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.
5 *Preparative Chemistry Using Supported Reagents*, ed. P. Laszlo, Academic Press, London, 1987.
6 W. Hölderich, M. Hess and F. Näumann, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 226.
7 K. Smith, *Bull. Soc. Chim. Fr.*, 1989, 272; *Organic Synthesis Using Solid Supports and Catalysts*, ed. K. Smith, Ellis Horwood, Chichester, 1992; K. Smith, in *New Aspects of Organic Synthesis II*, ed. Z. Yoshida and Y. Ohshiro, Kadansha, Tokyo and VCH, Weinheim, 1992, p. 43; L. Delaude, P. Laszlo and K. Smith, *Acc. Chem. Res.*, 1993, **26**,

607; K. Smith, in *Catalysis of Organic Reactions*, ed. M. G. Scaros and M.L. Prunier, Marcel Dekker, New York, 1995, p. 91.

8 H. van Bekkum, E. M. Flanigen and J. C. Jansen, *Stud. Surf. Sci. Catal*., 1991, **58**.

9 R. A. Grey, US Patent 4 731 479, 1988; *Chem. Abstr*., 1988, **109**, 57043q.

10 K. Smith, M. Butters, W. E. Paget and B. Nay, *Synthesis*, 1985, 1155; K. Smith, M. Butters and B. Nay, *Synthesis*, 1985, 1157; *Tetrahedron Lett*., 1988, **29**, 1319; A. G. Mistry, K. Smith and M. R. Bye, *Tetrahedron Lett*., 1986, **27**, 1051; K. Smith, D. M. James, A. G. Mistry, M. R. Bye and D. J. Faulkner, *Tetrahedron*, 1992, **48**, 7479; K. Smith, D. M. James, I. Matthews and M. R. Bye, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1877.

11 K. Smith, K. B. Fry, M. Butters and B. Nay, *Tetrahedron Lett*., 1989, **30**, 5333; K. Smith and K. B. Fry, *J. Chem. Soc., Chem. Commun*., 1992, 187; K. Smith and D. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1992, 407; K. Smith and D. Bahzad, *Chem. Commun*., 1996, 467; K. Smith, A. Musson and G. A. Deboos, *Chem. Commun*., 1996, 469; K. Smith and D. Bahzad, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2793.

12 For a preliminary communication of some of these results, see K. Smith and G. M. Pollaud, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3519.

13 S. H. Sharman, *J. Am. Chem. Soc*., 1962, **84**, 2945.

14 I. Mochida, K. Takeshita, M. Ohgai and T. Seiyama, *Ind. Eng. Chem. Prod. Res. Dev*., 1980, **19**, 392.

15 T. J. Lovelock, Ph.D. Thesis, University of Wales Swansea, 1990.

16 See, *e.g*. P. Laszlo and A. Mathy, *Helv. Chim. Acta*, 1987, **70**, 577; J. H. Clark, A. P. Kybett, D. J. Macquarrie, S. J. Barlow and P. Landon, *J. Chem. Soc., Chem. Commun*., 1989, 1353; S. J. Barlow, J. H. Clark, M. R. Darby, A. P. Kybett, P. Landon and K. Martin, *J. Chem. Res*. (S), 1991, 74.

17 A.I. Kakhniashvili and E.N. Chikovani, *Soobshch. Akad. Nauk Gruz. SSR*, 1969, **53**, 93; *Chem. Abstr*., 1969, **71**, 80841d.

18 A. I. Kakhniashvili and E. N. Chikovani, *Soobshch. Akad. Nauk Gruz. SSR*, 1968, **52**, 367; *Chem. Abstr*., 1969, **70**, 106143j.

19 A. I. Kakhniashvili and D. Ya. Bugianishirli, *Zh. Org. Khim*., 1965, **1**, 1043; *J. Org. Chem. USSR*, 1965, **1**, 1051.

20 B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Wiley, New York, 1989.

21 G. M. Pollaud, Ph.D. Thesis, University of Wales Swansea, 1992.

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# Selective mono-chlorination of aromatic compounds

## under mild conditions by *tert*-butyl hypochlorite in the presence of zeolites

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## Summary

*tert*-Butyl hypochlorite/HNa faujasite X in acetonitrile represents an efficient and highly regioselective system for mono-chlorination of a wide range of mono- and di-substituted aromatic substrates in mild conditions. Partially protonated faujasite X is far superior to amorphous silicas and to other zeolites in terms of efficiency and regioselectivity. Advantages of *tert*-butyl hypochlorite over other chlorinating reagents have been demonstrated. The method is suitable for large scale work.

## Introduction

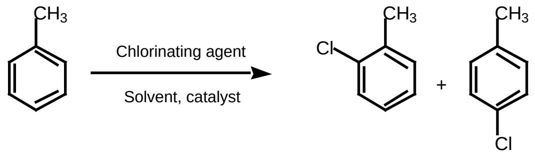
Owing to their numerous applications as fine chemicals for the synthesis of bio-active compounds such as pesticides and pharmaceuticals, isomerically pure chloroaromatics are very valuable materials. Unfortunately, the usual methods for chlorination of aromatics lead in many cases to mixtures of regioisomers that are difficult to separate. This leads to loss of material and waste of both time and energy. A further disadvantage is the use of a catalyst such as aluminium chloride, which is destroyed during work-up, produces a corrosive acid by-product, and presents a disposal problem. Therefore, there is a considerable need to devise reactions that avoid the use of such Lewis acid catalysts and provide greater regioselectivity in order to offer opportunities for much more environmentally benign processes.

Within recent decades, considerable efforts have been expended on the development of more efficient and selective aromatic chlorination processes,[1,2] but many problems remain, especially for simple compounds such as toluene. As part of our own studies on the use of solid supports in catalysing electrophilic aromatic substitution reactions,[3] we have investigated chlorination over heterogeneous catalysts[4] as an attractive approach to chloroaromatics. We now report details of a chlorination reaction that makes use of the shape selective properties of a reusable zeolite catalyst to provide remarkable *para*-selectivity, thereby overcoming two of the major disadvantages of the traditional approach.

## Results and discussion

### Chlorination over silicas

Our initial interest in the use of silica as a support arose from an experimental observation that purification on BDH silica of a crude reaction mixture containing dichloramine-T (DCT) led to the formation of some chlorinated side-products that were not present originally.[5] Toluene was used as a substrate [eqn. (1)] in



(1)

order to probe the factors that influence the reaction and various reagents were screened for their ability to perform electrophilic chlorinations.

The results, summarised in Table 1, clearly showed that, with silica as a catalyst, DCT, *N*,*N*-dichlorourethane, *tert*-butyl hypochlorite and $SO_2Cl_2$ were the reagents of most promise. In each case, the regioselectivity (65% *ortho* : 35% *para*) reflected the relative proportions of *ortho* to *para* positions in toluene (*i.e.* 2:1). Several acid chlorides (benzoyl chloride, oxalyl chloride, butyl chloroformate, tosyl chloride), metal chlorides (LiCl, $BCl_3$, $AlCl_3$, $HgCl_2$, $TiCl_4$) and other chlorine-containing compounds ($POCl_3$, $SOCl_2$, chloramine-T, $Et_2NCl$, chloroacetone, α-chloroacetamide) showed negligible reaction under these conditions even after a considerable period of time (*ca.* 2 days).

## Green Context

**Zeolites have found relatively little use in the liquid phase synthesis of organic compounds due to their small pore size and related diffusional limitations. However, in some cases, they offer unique advantages in terms of excellent selectivity towards mono substitution and positional isomerism. Exceptionally high selectivity is an essential requirement for the synthesis of precursors to many bioactive compounds. The combination of a bulky chlorinating agent and a zeolite has been shown to be an effective methodology in this respect. *DJM***

**Table 1** Chlorination of toluene according to eqn. (1)[a]

| Reagent | Time of reaction/h | Yield of chlorotoluenes (%)[b] |
|---|---|---|
| Dichloramine-T (DCT) | 4 | 100 |
| $PCl_3$ | 72 | 10 |
| *N*,*N*-Dichlorourethane | 2 | 100 |
| *N*-Chlorosuccinimide | 48 | 15 |
| $SO_2Cl_2$ | 0.5 | 100[c] |
| $HgO/Cl_2$ | 2 | 'High'[d,e] |
| *t*-BuOCl | 1 | 100 |
| $H_2O/Ca(OCl)_2$ | 12 | 60[d] |
| $Cl_2NPO(OEt)_2$ | 4 | 'High'[d,f] |
| NaOCl | 12 | 60[d] |

[a] Toluene (2.5 mmol), chlorinating agent (2.5 mmol) in tetrachloromethane (10 ml) over silica (3 g) at 20°C. [b] By quantitative GC. [c] 3.5 mmol of chlorinating agent used. [d] A large excess of reagent was used. [e] Large amounts of polychlorinated compounds formed. [f] Initial preparation of the reagent proved hazardous (very exothermic).

Of the two most reactive chlorinating agents ($SO_2Cl_2$ and *t*-BuOCl), only sulfuryl chloride had been used in conjunction with silica previously.[6] The two reagents were compared more critically and sulfuryl chloride proved to be much more sensitive to the physical form of the silica than *tert*-butyl hypochlorite. Table 2 depicts the results obtained in equimolar reactions between toluene and the two chlorinating agents in tetrachloromethane at room temperature. The results suggest that a small amount of water is needed to catalyse the reaction with the former reagent while too much water leads to its decomposition. In contrast, *tert*-butyl hypochlorite appears to be much more stable in the presence of water although the rate of the reaction is decreased in the presence of extra water. This factor, together with the undesirable evolution of HCl and $SO_2$ from $SO_2Cl_2$, made *tert*-butyl hypochlorite the more attractive chlorinating reagent and it was chosen for a more detailed study of the reaction.

**Table 2** Comparison of $SO_2Cl_2$ and *t*-BuOCl using treated silica in reaction (1)[a]

| Reagent | Pre-treatment of silica | Time of reaction/h | Yield of chlorotoluenes (%)[b] |
|---|---|---|---|
| $SO_2Cl_2$ | None[c] | 0.5 | 70 |
| $SO_2Cl_2$ | Extra 1% (w/w) of water | 0.5 | 1 |
| | | 48 | 30 |
| $SO_2Cl_2$ | Dried at 540 °C for 15 h | 24 | 25 |
| *t*-BuOCl | None[c] | 0.5 | 60 |
| | | 1 | 100 |
| *t*-BuOCl | Extra 1% (w/w) of water | 0.5 | 2 |
| | | 48 | 95 |

[a] Toluene (2.5 mmol), chlorinating agent (2.5 mmol) in tetrachloromethane (10 ml) over silica (3 g) at 20°C. [b] By quantitative GC. [c] As supplied in a freshly opened bottle of chromatographic grade silica (BDH); contains a small amount of water.

Table 3 reports the influence of solvent on the outcome of the reaction. It appears that the *para* selectivity of the reaction is slightly increased in polar solvents, but relatively non-polar solvents give faster reactions and higher yields. The rate differences might be explained on grounds of more effective solvation of reactants and competitive adsorption of polar solvent molecules at catalytic sites. The particularly low yield in diethyl ether probably reflects a competitive reaction with the solvent. An experiment in tetrachloromethane, in which a small quantity of the powerful free radical scavenger galvinoxyl was added, gave the same result as without, and therefore suggested that free radicals are not involved in the reaction.

**Table 3** Influence of solvent in reaction (1)[a]

| Solvent | Time of reaction/h | Yield of chlorotoluenes (%) | *para*:*ortho* |
|---|---|---|---|
| $CCl_4$ | 1 | 100 | 35:65 |
| $CH_2Cl_2$ | 1 | 100 | 35:65 |
| $Et_2O$ | 24 | 5 | 35:65 |
| $PhNO_2$ | 24 | 70 | 37:63 |
| $CH_3OH$ | 2.5 | 100 | 43:57 |
| $CH_3CN$ | 24 | 60 | 50:50 |

[a] Toluene (5 mmol), *t*-BuOCl (5 mmol), solvent (10 ml), silica (3.67 g) at 25 °C.

In order to gain insight into the role played by the silica, reactions were carried out with a range of silicas from different sources and after treatment of the silicas in various ways. The silicas were also characterised to some extent by measurement of the pH they generated in an aqueous slurry and by their mean pore diameters. The results are listed in Table 4.

From the results in Table 4, it can be seen that reaction occurred most readily with silicas that were quite acidic (pH of a 10% aqueous slurry <5). The successful silicas were also the ones with smaller mean pore diameters, so that it is possible that the presence of micropores (<20 Å) in such silicas might also enhance the reaction by bringing the reagents into closer proximity. Water had a major effect on the activity of the silica, as evidenced by the slower reaction of BDH silica to which water had been added. The deactivating effect of excess water was again brought into focus by the case of Mallinckrodt silicic acid. The untreated silica was from a very old bottle and had absorbed a significant quantity of water. It was totally unreactive in that state, but after drying became almost as active as the BDH silica.

Since the combination of BDH silica and *tert*-butyl hypochlorite in tetrachloromethane provided a reagent capable of quantitative chlorination of toluene within one hour at 20 °C, it was of interest to test the scope of this reagent system with different substrates. A range of simple aromatic compounds was therefore investigated [eqn. (2)]. The results are shown in Table 5.

$$\mathrm{Ar{-}H} \xrightarrow[\mathrm{CCl_4,\ Silica}]{t\text{-}\mathrm{BuOCl}} \mathrm{Ar{-}Cl} \qquad (2)$$

The reaction was very slow for substrates less active than benzene, but useful for those with an activity level between that of about benzene and that of about anisole, cleanly producing chlorinated aromatics in about the same proportions as in traditional aromatic chlorination reactions. With yet more reactive substrates, *tert*-butyl hypochlorite reacted readily even in the absence of silica, so that the silica had little effect on the outcome of the reactions. Aniline was so reactive that it produced only tarry products under comparable conditions.

**Table 4** Influence of the nature of the silica in reaction (1)[a]

| Silica | Treatment[b] | pH[c] | Mean pore diameter/Å[d] | Time of reaction/h | Yield of chlorotoluenes (%)[e] | *para:ortho* |
|---|---|---|---|---|---|---|
| Shell | None | 7.4 | 200 | 24 | Trace | — |
| | A | n.d. | n.d. | 24 | Trace | — |
| Davison 57 | None | 7.1 | 146 | 24 | Trace | — |
| | B | 6.9 | n.d. | 24 | 10 | 35:65 |
| Kieselgel 60 | None | 6.9 | 58 | 24 | 5 | — |
| | A | n.d. | n.d. | 24 | 0 | — |
| | B | 6.2 | n.d. | 2 | 80 | 40:60 |
| Kieselgel 60G | None | 5.8 | 58 | 20 | 80 | 44:56 |
| Mallinckrodt | None | 5.3 | 34 | 72 | 0 | — |
| | B | 4.5 | n.d. | 2 | 100 | 35:65 |
| BDH | None | 4.7 | 18 | 1 | 100 | 35:65 |
| | C | n.d. | n.d. | 48 | 95 | 35:65 |

[a] Toluene (5mmol), *t*-BuOCl (5 mmol), silica (3.67 g), in tetrachloromethane (10 ml) at 20 °C. [b] The following methods of treatment were used: A, reflux in a 1 M solution of $NH_4Cl$ for one hour; calcination in a 520 °C furnace for 15 hours; B, drying in a 150 °C oven for 48 hours; C, 1% (w/w) water added. [c] pH meter reading of a 10% w/w slurry in deionized water; n.d. means not determined. [d] Determined by nitrogen BET adsorption isotherm; n.d. means not determined. [e] By quantitative GC.

**Table 5** Chlorination of aromatic substrates with *t*-BuOCl in $CCl_4$ according to eqn. (2)[a]

| Substrate | Temperature/°C | Time of reaction/h | Conversion of substrate (%)[b] | Product distribution (%)[b,c] |
|---|---|---|---|---|
| PhH | 50 | 72 | 80 | mono:dichloro = 81:19 |
| PhMe | 25 | 1 | 100 | *para*:*ortho* = 35:65 |
| PhEt | 25 | 144 | 86 | *para*:*ortho* = 43:57 |
| Ph*i*-Pr | 25 | 192 | 75[d] | *para*:*ortho* = 56:44 |
| Ph*i*-Pr | 40 | 4 | 97 | *para*:*ortho* = 53:47 |
| Ph*t*-Bu | 25 | 120 | 70[d] | *para*:*ortho* = 85:15 |
| PhPh | 25 | 96 | 70[d] | *para*:*ortho* = 44:56 |
| Naphthalene | 40 | 3 | 93 | α:β = >99:<1 |
| *p*-Xylene | 25 | 1 | 78 | mono:dichloro = 67:33 |
| PhOMe | 25 | 0.7 | 100 | *para*:*ortho* = 70:30 |
| PhOH | 25 | 0.1 | 100 | n.d. |
| PhNHAc | 25 | 0.1 | 100 | n.d. |
| PhCl | 50 | 96 | low | n.d. |
| PhBr | 60 | 24 | 15 | n.d. |
| $PhNO_2$ | 40 | 120 | 0 | — |

[a] Substrate (5 mmol), *t*-BuOCl (5 mmol), BDH silica (3.67 g), tetrachloromethane (10 ml) under the stated conditions. [b] By quantitative GC. [c] n.d. means not determined. [d] The reaction could be brought to completion within 2 to 4 more days by further addition of *tert*-butyl hypochlorite.

Although an acidic silica had proved to be capable of catalysing the reaction of *tert*-butyl hypochlorite with aromatic substrates of moderate activity, it provided little benefit in terms of regioselectivity of the reactions. Zeolites are capable of both stronger surface acidity and enhancing regioselectivity through exerting shape-selectivity within their pores. Therefore it was of interest to investigate the use of zeolites as catalysts in the new chlorination reaction.

## Chlorination over zeolites

Zeolites are well-defined, crystalline microporous aluminosilicates with active sites embedded within pores or cavities of molecular dimensions.[7] They are capable of acting as powerful acid catalysts and also providing selectivity for *para*-isomer production in aromatic substitution reactions. Recent papers have reported liquid-phase chlorination of aromatic substrates over zeolites using either chlorine[8] or sulfuryl chloride[9] as the electrophilic chlorine source, but selectivity in the reactions of simple substrates like toluene remains a problem. The chlorination of toluene by *tert*-butyl hypochlorite over various zeolites was therefore investigated and the results are presented in Table 6.

Silicalite, which does not have acidic sites, generated no ring-chlorinated products, although a substantial amount of benzyl chloride was formed after a long reaction period. The small pore A-type zeolite and those other zeolites which were not proton-exchanged (*i.e.* NaZSM-5, KL and NaX) provided little or no catalysis of the reaction so that the yields of chlorinated products were low even after several days. The proton-exchanged forms of ZSM-5, L and mordenite zeolites were somewhat better catalysts, but reactions were still slow and the *para*-selectivity, though somewhat greater than with silica as catalyst, was not remarkable, suggesting that most of the reaction was catalysed by sites

**Table 6** Chlorination of toluene according to eqn. (1) at 25 °C in tetrachloromethane using *tert*-butyl hypochlorite over zeolite catalysts[a]

| Zeolite | Pore size/Å | Time of reaction/h | Conversion of toluene (%)[b] | Products and distribution[b] |
|---|---|---|---|---|
| HCaA | 4.5 | 24 | 0 | — |
| NaZSM-5 | 5.2–5.4 | 120 | 7 | 52% *p*-Chlorotoluene<br>48% Dichlorotoluenes |
| HNaZSM-5 | 5.4–5.6 | 36 | 20 | 47% *p*-Chlorotoluene<br>53% *o*-Chlorotoluene |
| Silicalite-1 | 5.5 | 96 | 30 | 100% Benzyl chloride |
| HNaMordenite | 6.7–7.0 | 72 | 15 | 40% *p*-Chlorotoluene<br>60% *o*-Chlorotoluene |
| KL | 7.0 | 48 | 0 | — |
| HKL | 7.1 | 48 | 25 | 56% *p*-Chlorotoluene<br>44% *o*-Chlorotoluene |
| NaX | 7.4 | 72 | 11 | 65% *p*-Chlorotoluene<br>35% *o*-Chlorotoluene |
| HNaX | 7.5 | 1 | 90 | 65% *p*-Chlorotoluene<br>35% *o*-Chlorotoluene |

[a] Toluene (2.5 mmol), *t*-BuOCl (2.5 mmol), zeolite (1.5 g), tetrachloromethane (10 ml) at 25°C. [b] By quantitative GC.

on the external surfaces of the solids rather than within the pores. Only partially proton-exchanged faujasite X (HNaX) proved to be an efficient catalyst, producing almost quantitative ring chlorination within one hour at 25°C. This result is consistent with the fact that faujasite has the largest pore diameter of all the zeolites tried (the more restricted profile of toluene, in a planar view, measures roughly 5.8 Å) and also has a three dimensional lattice structure with many interconnecting cavities of even greater dimensions, so that diffusion of substrate and reagents through the pores is relatively easy. The selectivity obtained was moreover a complete contrast to that achieved over silica gel in the same conditions and thus indicated that a change of support has a remarkable effect upon the regioselectivity of the reaction, again consistent with the idea that reaction takes place within the inner cavities of the zeolite.

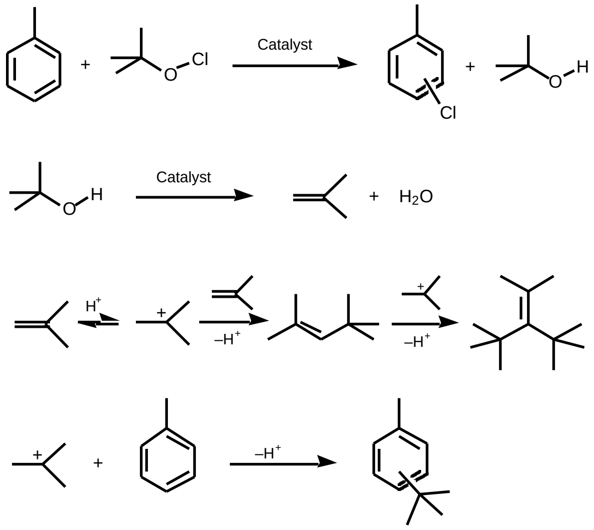
Since the faujasite zeolite had proved to be such an active catalyst, it was investigated in more detail to see if manipulation of its structural parameters could further influence the reaction in a positive manner. Thus, a series of experiments was performed with catalysts for which the Si : Al ratio of the material varied over the range 1.23 to 2.40:1 (Table 7).

**Table 7** Effect of the variation of the Si : Al ratio of faujasite catalysts on the chlorination of toluene by *tert*-butyl hypochlorite according to eqn. (1)[a]

| Si:Al | Time of reaction/h | Conversion of toluene (%)[b] | *para*:*ortho* | By-products present |
|---|---|---|---|---|
| 1.23 | 0.25 | 90 | 73:27 | No |
| 1.53 | 0.25 | 80 | 72:28 | No |
| 1.82 | 0.25 | 50 | 62:38 | Yes |
| 2.11 | 4 | 42 | 54:46 | Yes |
| 2.40 | 6 | 40 | 42:58 | Yes |

[a] Toluene (2.5 mmol), *t*-BuOCl (2.5 mmol), faujasite zeolite (1.5 g), tetrachloromethane (10 ml) at 25 °C. [b] By quantitative GC.

Faujasite zeolites are referred to as zeolite X when the Si : Al ratio is ⩽1.5 and zeolite Y when the ratio is >1.5. The results showed that as the Si : Al ratio increased, the amount of chloroaromatics formed and the *para*-regioselectivity dropped off. Instead, the *tert*-butyl hypochlorite was consumed in side-reactions leading to *tert*-butyltoluene and isobutene oligomers (Scheme 1).



**Scheme 1** Side-reactions in the chlorination of toluene by *tert*-butyl hypochlorite over HNaY.

The alkylation side-reaction is analogous to the one occurring on benzene in the presence of $AlCl_3$[10] and reflects the fact that HY is more strongly acidic than HX. Whatever the precise reasons for the change, it was clear that zeolite HX was the optimum catalyst and it was studied further. The effect of different solvents was next investigated and the results are given in Table 8.

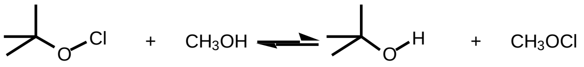
The results clearly showed that there was no simple correlation with solvent polarity.[11] Good yields of monochlorotoluenes were obtained in a non-polar solvent such as pentane and in a very polar solvent like acetonitrile. Solvents having a strongly co-ordinating functionality (amines and DMF) tended to deactivate the acid sites of the zeolite and so to inhibit the reaction completely. The slow reaction rate and the low selectivity observed in methanol may reflect the fact that methanol is also capable of

**Table 8** Effect of solvent on the chlorination of toluene over partially protonated X zeolite by *tert*-butyl hypochlorite at room temperature[a]

| Solvent | Time of reaction/h | Conversion of toluene (%)[b] | *para*:*ortho*[b] |
|---|---|---|---|
| *n*-Pentane | 1 | 78 | 63:37 |
| Toluene | 28 | — | 71:29 |
| $CH_2Cl_2$ | 1 | 95 | 74:26 |
| $CCl_4$ | 1 | 95 | 74:26 |
| $Et_2O$ | 0.5 | 63 | 92:8 |
| $CH_2Cl_2$: $Et_2O$ (3:1) | 1 | 95 | 91:9 |
| 1,4-Dioxane | 1 | 0 | — |
| THF | 1 | 0 | — |
| 1,2-Dimethoxyethane | 1 | 0 | — |
| DMF | 24 | 5 | 50:50 |
| $CH_3CN$ | 0.5 | 100 | 82:18 |
| $CH_3OH$ | 20 | 46 | 40:60 |
| TMEDA | 24 | 0 | — |
| Piperidine | 24 | 0 | — |
| Pyridine | 24 | 0 | — |

[a] Toluene (2.5 mmol), *t*-BuOCl (2.5 mmol), HX (1.5 g), solvent (10 ml) at 25 °C. [b] By quantitative GC.

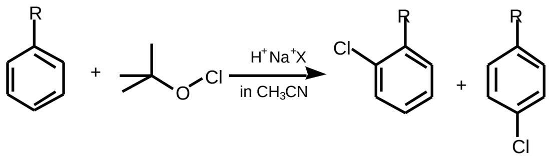
forming strong hydrogen bonds with the acid sites of the faujasite pores, diminishing their activity and also inhibiting diffusion of reactants in and out of the lattice. However, chlorine exchange to give the less hindered methyl hypochlorite [eqn. (3)] might also play a role.



(3)

It appeared quite remarkable that from the selection of ethers tried, only diethyl ether produced any chlorotoluenes, but with outstanding *para*-selectivity. However, the modest yield (63%) was accounted for by a side reaction of the chlorinating reagent system with the ether. Presumably, therefore, the more reactive ethers completely consumed all of the *tert*-butyl hypochlorite in a similar way. The high regioselectivity (92% *para*) obtained in diethyl ether probably depends on a delicate interplay of factors, such as the geometrical flexibility and electron density distribution in diethyl ether, which may render it capable within the pores of stabilising the *tert*-butyl hypochlorite oxonium cation that is likely to be involved in the reaction mechanism.[12] The benefits of high regioselectivity in diethyl ether and high yield in dichloromethane could be combined by use of a mixture of the two solvents ($CH_2Cl_2$:$Et_2O$ = 3:1), which gave a 95% yield of monochlorotoluenes as a 91:9 mixture of *para* and *ortho* isomers. However, even this mixture caused some decomposition of the hypochlorite and its use with any substrate less active than toluene would not be practical.

In view of the problems with the possible use of diethyl ether for many substrates, acetonitrile appeared to be the best solvent for development of a general procedure. It was thus used with a series of monosubstituted aromatic compounds [eqn. (4)] and the results are shown in Table 9.



(4)

**Table 9** Chlorination of substituted benzenes with *tert*-butyl hypochlorite over HNaX in acetonitrile according to eqn. (4)[a]

| R | Temp./°C | Time of reaction/h | Yield of product (%)[b] | Isomer distribution (*p*:*o*)[b] |
|---|---|---|---|---|
| OMe[d] | 25 | 3 | 100 | 82:18 |
| Me | 25 | 1 | 100 | 82:18 |
| H | 40 | 3.5 | 92[c] | — |
| Et | 40 | 3.5 | 100 | 90:10 |
| *i*-Pr[e] | 40 | 96 | 90 | 80:20 |
| *t*-Bu[e] | 40 | 96 | 99 | 98:2[f] |
| Ph[e] | 45 | 72 | 86 | 86:14 |
| Cl | 40 | 120 | 95 | 97:3 |
| Br | 40 | 96 | 75 | 97:3 |

[a] Substrate (2.5 mmol), *t*-BuOCl (2.5 mmol), $CH_3CN$ (10 ml), HX (1.5 g) under the stated conditions. [b] By quantitative GC. [c] Product was 92% chlorobenzene and 4% dichlorobenzene. [d] Anisole could be chlorinated by *tert*-butyl hypochlorite without zeolite within 4 hours with the same regioselectivity. [e] *tert*-Butyl hypochlorite was added in two portions, half at the beginning and half mid-way through the reaction period. [f] The *ortho* and *meta* isomers could not be separated so the figure for *ortho* may include a trace of *meta* isomer.

As shown in Table 9 the reaction was successful with a range of aromatic substrates of moderate activity, ranging from about anisole at the most active end to halogenobenzenes at the less active limit. Yields and *para*-selectivities were excellent although the reactions with the less active substrates were rather slow. Furthermore, the reaction was shown to be suitable for larger scale work by the preparations of *para*-chlorotoluene and *para*-dichlorobenzene on 0.1 mole scale without any detrimental effects on either the yield or the selectivity. Benzonitrile, nitrobenzene, benzoic acid and methyl benzoate were also tested, but gave no significant reaction over a period of 3 days at 40 °C.

In view of the lack of success in chlorination of toluene over zeolites other than HX, even other large pore zeolites, it was likely that the transition state for the reaction was taking up most of the space within the cavity of the HX zeolite. Indeed, it was likely that the geometrical constraints imposed as a result were in large part responsible for the impressive regioselectivity. Therefore, it was by no means certain that disubstituted benzenes would react at all readily with *tert*-butyl hypochlorite over zeolite HX. Nevertheless, following the success with monosubstituted benzenes, the new reaction system comprising *tert*-butyl hypochlorite and HX zeolite in acetonitrile was applied to a range of disubstituted aromatics. The results are shown in Table 10.

As the results in Table 10 show, none of the disubstituted substrates reacted readily with *tert*-butyl hypochlorite over zeolite HX. The low rates of reaction were particularly remarkable for the xylenes, which are quite highly activated substrates, and for the two *para*-substituted compounds (*para*-xylene and *para*-chlorotoluene), where there would be negligible inhibition to diffusion of the substrates. In the case of *para*-chlorotoluene the conversion was only 11% after 10 days at 40 °C even though the *tert*-butyl hypochlorite level was regularly replenished. These results are very strongly suggestive of transition state selectivity at the acidic catalytic sites of the zeolite. In the case of disubstituted benzenes with such slow reactions, it must be expected that

**Table 10** Chlorination of disubstituted aromatic compounds by *tert*-butyl hypochlorite in acetonitrile in the presence of HNaX[a]

| Substrate | Temp./°C | Time of reaction/days | Conversion of substrate (%)[b] | Chlorinated products [Yields (%)][b] |
|---|---|---|---|---|
| *o*-Chlorotoluene | 20 | 15[c] | 100 | 2,5-Dichlorotoluene [61]<br>2,4-Dichlorotoluene [22]<br>2,6-Dichlorotoluene [1] |
| *o*-Chlorotoluene | 40 | 10[c] | 100 | 2,5-Dichlorotoluene [59]<br>2,4-Dichlorotoluene [21]<br>2,6-Dichlorotoluene [10] |
| *o*-Chlorotoluene[c] | 40 | 4 | 100 | 2,5-Dichlorotoluene [50]<br>2,4-Dichlorotoluene [26]<br>2,6-Dichlorotoluene [6] |
| *m*-Chlorotoluene | 20 | 18[c] | 100 | 2,5-Dichlorotoluene [66]<br>3,4-Dichlorotoluene [24] |
| *m*-Chlorotoluene | 40 | 10[c] | 100 | 2,5-Dichlorotoluene [61]<br>3,4-Dichlorotoluene [22] |
| *p*-Chlorotoluene | 40 | 10[c] | 11 | 2,4-Dichlorotoluene [9] |
| *o*-Xylene | 20 | 4 | 100 | 4-Chloro-*o*-xylene [70]<br>3-Chloro-*o*-xylene [9] |
| *o*-Xylene | 40 | 1 | 94 | 4-Chloro-*o*-xylene [60]<br>3-Chloro-*o*-xylene [11]<br>Polychloro-*o*-xylenes [6] |
| *m*-Xylene | 20 | 4 | 100 | 4-Chloro-*m*-xylene [82]<br>2-Chloro-*m*-xylene [8] |
| *m*-Xylene | 40 | 1 | 97 | 4-Chloro-*m*-xylene [67]<br>2-Chloro-*m*-xylene [7]<br>Polychloro-*m*-xylenes [3] |
| *p*-Xylene | 40 | 1 | 90 | 2-Chloro-*p*-xylene [73]<br>Polychloro-*p*-xylenes [10] |
| Naphthalene | 20 | 8 | 25 | 1-Chloronaphthalene [16]<br>2-Chloronaphthalene [2] |
| Naphthalene | 40 | 5 | 64 | 1-Chloronaphthalene [44]<br>2-Chloronaphthalene [9]<br>Polychloronaphthalene [1] |
| *o*-Chloroanisole | 20 | 10[c] | 100 | 2,4-Dichloroanisole [82] |
| *o*-Chloroanisole | 40 | 7[c] | 100 | 2,4-Dichloroanisole [88] |

[a] Substrate (2.5 mmol), *t*-BuOCl (2.5 mmol), $CH_3CN$ (10 ml), HX (1.5 g) under the stated conditions. [b] Yields and product distributions were determined by 400 MHz NMR, GC, and GC-MS. [c] *tert*-Butyl hypochlorite was added during the course of the reaction as it decomposes with time. [d] The reaction was carried out with three molar equivalents of *tert*-butyl hypochlorite.

a significant part of the reaction that does actually occur takes place on the external surface rather than within the pores.

Notwithstanding the above, most disubstituted aromatics tried could eventually be chlorinated in high yield with moderate to excellent selectivities. Slightly deactivated *ortho*- and *meta*-chlorotoluenes gave predominantly chlorination *para* to one of the substituents with a substantial preference for substitution *para* to chlorine. *para*-Chlorotoluene was very selectively chlorinated *ortho* to the methyl group but the very low rate of the reaction makes it impractical for synthetic purposes. More activated *ortho* and *meta*-xylenes gave good *para*-selectivity (*ca.* 90% at 20 °C), but heating the reaction mixture to 40°C led to the emergence of unwanted polychlorinated compounds. *para*-Xylene afforded 2-chloro-*p*-xylene together with polychlorinated aromatics at 40°C. Finally, naphthalene was chlorinated only to the extent of 65% after 5 days at 40 °C. Although the selectivity obtained was higher for the 2-chloro isomer than that achieved on silica, it was not sufficient for synthetic purposes. *ortho*-Chloroanisole was very selectively (*ca.* 100%) chlorinated *para* to the methoxy moiety and the zeolite provided a genuine catalytic effect on the reaction as a control reaction performed without the zeolite showed a ten times lower rate.

In view of the slowness of the reactions of disubstituted benzenes with *tert*-butyl hypochlorite over zeolite HX, attention was turned again to sulfuryl chloride which had proved to be a more reactive if more troublesome reagent over silica as catalyst (see above). Former work carried out on chlorination over zeolites by sulfuryl chloride had made use of basic forms of the solids and led to side-chain chlorination.[9] In the present study partially proton-exchanged zeolites were used. Toluene was again chosen as the test substrate and a survey of several zeolites for its chlorination by excess sulfuryl chloride was conducted. The results are shown in Table 11.

A significant yield of chlorination products was encountered at room temperature within one hour only for the faujasite zeolites X and Y and those reactions gave the same products whether in dark conditions or not. HNaX was once more the zeolite of most interest. There was only a trace of *meta*-product and no observable amount of side-chain chlorinated products, in sharp contrast to the results observed with its sodium form.[9] Furthermore, the reaction showed some regioselectivity. It was thereafter observed that good conversions could be obtained with just three molar equivalents of the chlorinating reagent in either dry petroleum spirit (30–40 °C) or dry dichloromethane. Therefore, a study of different solvents was carried out (Table 12).

**Table 11** Chlorination of toluene over partially proton-exchanged zeolites by sulfuryl chloride according to eqn. (1)[a]

| Zeolite | Conversion of toluene (%)[b] | Yield of *o*-chloro-toluene (%)[b] | Yield of *p*-chlorotoluene (%)[b] |
|---|---|---|---|
| HNaβ | <5 | 2.0 | 1.2 |
| HNaZSM-5 | 0 | 0 | 0 |
| HNaMord | <5 | 1.5 | 0.8 |
| HNaY 760[c] | <5 | 1.8 | 0.8 |
| HNaY 500[c] | 24 | 11 | 6 |
| HNaY 712[c] | 76 | 48 | 21 |
| HNaX | 100[d] | 34 | 48 |

[a] Toluene (2.5 mmol), $SO_2Cl_2$ (12.5 mmol), zeolite (1.5 g), $CH_2Cl_2$ (10 ml), 20°C, 1 h. [b] By quantitative GC. [c] Refs. to Si:Al ratios of 60.3, 10.5 and 5.5 for HNaY 760, HNaY 712 and HNaY 500 respectively. [d] 10% Polychlorinated compounds also observed.

**Table 12** Effect of the solvent on the chlorination of toluene over HNaX by sulfuryl chloride according to eqn. (1).[a]

| Solvent | Conversion of toluene (%)[b] | Yield of chloro-toluenes (%)[b] | *p*:*o*[b] |
|---|---|---|---|
| $CH_2Cl_2$ | 100 | 84[c] | 58:42 |
| $CH_3CN$ | 69 | 59 | 65:35 |
| $CH_3NO_2$ | 70 | 68 | 57:43 |
| $Et_2O$ | 5 | 3 | 89:11 |
| THF | 0 | 0 | — |
| Pet.Sp.[d] (30–40 °C) | 100 | 82[e] | 60:40 |
| $CH_2Cl_2$:$CH_3CN$ (1:1) | 28 | 20 | 69:31 |
| DME | 5 | 1 | 63:37 |
| Pet.Sp. (80–100 °C) | 27 | 18 | 60:40 |
| $CH_2Cl_2$:$Et_2O$ (1:1) | 19 | 12 | 86:14 |
| $CH_2Cl_2$:$Et_2O$ (4:1) | 51 | 32 | 85:15 |
| $CH_2Cl_2$:$Et_2O$ (9:1) | 63 | 42 | 83:17 |
| $CH_2Cl_2$:$Et_2O$ (49:1) | 71 | 53 | 65:35 |
| Pet.Sp. (30–40 °C):$Et_2O$ (1:1) | 27 | 13 | 87:13 |

[a] Toluene (2.5 mmol), $SO_2Cl_2$ (7.5 mmol), HX (1.5 g), solvent (10 ml), 20 °C, 1 h. [b] By quantitative GC. [c] 5% of polychlorinated products also formed. [d] Pet. Sp. = petroleum spirit. [e] 8% of polychlorinated products also formed.

The results in Table 12 show that the reaction is quite efficient in dichloromethane, light petroleum, acetonitrile and nitromethane, but selectivities are lower than with *tert*-butyl hypochlorite and excess reagent is needed. Tremendous regioselectivity could be achieved in anhydrous diethyl ether, but the conversion of toluene was very poor as the formation of a volatile by-product from the solvent and the chlorinating reagent consumed the reagent and may have poisoned the catalyst. Conversion of toluene increased if either petroleum spirit or dichloromethane was mixed with diethyl ether, but to the detriment of the *para*-selectivity. Overall, therefore, sulfuryl chloride proved inferior to *tert*-butyl hypochlorite again and was not studied further for reactions of disubstituted substrates.

## Conclusion

The present work shows that monochlorination of a wide range of aromatic substrates is feasible in mild conditions with good to excellent regioselectivity in the presence of zeolites. The best general system involves HNaX/*tert*-butyl hypochlorite in acetonitrile.

## Experimental

GC measurements were carried out on a Hewlett Packard 5890 Series II apparatus fitted with a 30 m long RTX-1 column (ID 0.32; DF 0.8) with microprocessor control (oven temperature programming, injector temperature 250 °C, FID detector temperature 300 °C). The head pressure of $N_2$ carrier gas was 8.5 psi. All quantifications of reaction constituents were achieved using a known quantity of dry decane as reference standard. This was added together with the reactants in all reactions. Oven temperature rampings were chosen in order to obtain ‘base line’ separation of all components in a mixture.

Sulfuryl chloride was distilled prior to use and the colourless fraction, bp 68–70°C, was collected. *tert*-Butyl hypochlorite was prepared using a standard procedure,[12] diluted in the dry solvent used for the reaction and estimated before use by iodometric titration. *N*,*N*-Dichloramine-T was obtained following an established method[13] and recrystallized before use. *N*,*N*-Dichlorodiethylphosphoramidate was prepared using a modification of a known procedure (sodium hypochlorite was used instead of chlorine gas).[14] *N*-Chlorodiethylamine was synthesised by a literature method.[15] Other chlorinating agents were commercial samples and required no further purification.

Solvents were purified and dried by standard techniques[16] before use. Commercial liquid and solid starting materials were respectively purified by fractional distillation or recrystallization before use. Dichloroanisoles were obtained from the corresponding commercial phenols following standard phase-transfer catalysed procedures.[17]

All silica gels and zeolites were obtained from a commercial source and dried respectively in an oven at 150 °C or a furnace at 400 °C. Partially proton-exchanged sodium zeolites were obtained by reflux for one hour in a 1 M ammonium chloride solution (10 ml for 1 g), filtration, washing with distilled water until the washings were chloride free, and then drying in a furnace at 500 °C.

### Chlorination over silica; general procedure

Solvent (10 ml), silica (3.76 g), decane (76 mg, as GC standard), aromatic substrate (5.0 mmol) and chlorinating agent (5.0 mmol) were gently stirred together at the stated temperature in a 50 ml round-bottomed flask. After completion of the reaction, the mixture was filtered and the silica was washed with more solvent. The combined filtrates were analysed on GC without any further purification.

### Chlorination over zeolite; *tert*-butyl hypochlorite procedure

Solvent (10 ml), zeolite (1.5 g), decane (76 mg, as GC standard), aromatic substrate (2.5 mmol) and *tert*-butyl hypochlorite (2.5 mmol) were gently stirred together at the stated temperature in a 50 ml round-bottomed flask. From time to time, aliquots were taken and filtered through cotton wool. The zeolite was washed with more solvent and the combined filtrates were analysed on GC without any further purification.

### Chlorination over zeolite; sulfuryl chloride procedure

Solvent (10 ml), zeolite (1.5 g), decane (76 mg, as GC standard), aromatic substrate (2.5 mmol) and sulfuryl chloride (7.5 or 12.5 mmol—see text) were gently stirred together at room temperature in a 50 ml round-bottomed flask. From time to time, aliquots were taken and filtered through cotton wool. The zeolite was washed with more solvent and the combined filtrates were analysed on GC without any further purification.

### Preparative chlorination of chlorobenzene using *tert*-butyl hypochlorite and HX

To partially proton-exchanged sodium faujasite X (20 g) was added acetonitrile (54 ml) and chlorobenzene (3.83 g, 34 mmol). In a separate vessel, *t*-BuOCl (34 mmol) was dissolved in acetonitrile (82 ml). This solution was added to the first mixture, the flask was fitted with a reflux condenser, and the mixture was heated to 40 °C in a thermostatically controlled water bath, whilst gentle stirring was maintained. After 14 days, the mixture was cooled and filtered. The separated solid was washed with more acetonitrile (50 ml), pentane (2 × 50 ml) and water (50 ml) and the combined filtrates were placed in a separating funnel. The pentane layer was separated and then washed with water (2 × 20 ml) and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure gave a white semi-solid material in almost quantitative yield. GC analysis showed the material to consist of 1,4-dichlorobenzene (97%) and 1,2-dichlorobenzene (3%). This material was further purified by kugelrohr distillation (*ca.* 55 °C/10 Torr) to give a colourless crystalline distillate which, according to GC analysis, was almost pure 1,4-dichlorobenzene containing just a trace of 1,2-dichlorobenzene; yield: 4.60 g (92%), mp = 50–51 °C (ref:[18] mp = 53°C).

## Acknowledgements

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## References

1 P. B. D. De la Mare, *Electrophilic Halogenation*, Cambridge University Press, Cambridge, 1976.

2 R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, 1989, p. 316; J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992, p. 531.

3 A. G. Mistry, K. Smith and M. R. Bye, *Tetrahedron Lett.*, 1986, **27**, 1051; K. Smith, M. Butters and B. Nay, *Tetrahedron Lett.*, 1988, **29**, 1319; K. Smith, K. Fry, M. Butters and B. Nay, *Tetrahedron Lett.*, 1989, **30**, 5333; K. Smith, *Bull. Soc. Chim. Fr.*, 1989, 272; K. Smith, *L'actualité chimique*, 1990, 205; K. Smith, in *Advances in Organobromine Chemistry 1*, ed. J.-R. Desmurs and B. Gérard, Elsevier, Amsterdam, 1991, p. 5; K. Smith, *Stud. Surf. Sci. Catal.*, 1991, **59**, 55; K. Smith and K. B. Fry, *J. Chem. Soc., Chem. Commun.*, 1992, 187; K. Smith and D. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1992, 407; K. Smith, D. M. James, A. G. Mistry, M. R. Bye and D. J. Faulkner, *Tetrahedron*, 1992, **48**, 7479; K. Smith, D. M. James, I. Matthews and M. R. Bye, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1877; K. Smith, in *New Aspects of Organic Synthesis II*, ed. Z. Yoshida and Y. Ohshiro, VCH, Weinheim, 1992, p. 43; L. Delaude, P. Laszlo and K. Smith, *Acc. Chem. Res.*, 1993, **26**, 607; K. Smith and G. Pollaud, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3519; K. Smith, in *Advances in Organobromine Chemistry II*, ed. J. R. Desmurs, B. Gérard and M. J. Goldstein, Elsevier, Amsterdam, 1995, p. 49; K. Smith, in *Catalysis of Organic Reactions*, ed. M. G. Scaros and M. L. Prunier, Marcel Dekker, New York, 1995, p. 91; K. Smith, C. V. Fry and M. Tzimas, in *Chemistry of Waste Minimisation*, ed. J. H. Clark, Blackie, London, 1995, p. 86; K. Smith and D. Bahzad, *Chem. Commun.*, 1996, 467; K. Smith, A. Musson and G. A. DeBoos, *Chem. Commun.*, 1996, 469; K. Smith, Z. Zhenhua, L. Delaude and P. K. G. Hodgson, *Stud. Surf. Sci. Catal.*, 1997, **108**, 99; K. Smith, Z. Zhenhua and P. K. G. Hodgson, *J. Mol. Catal. A*, 1998, **134**, 121.

4 Preliminary communications of some of the work were given previously: K. Smith, M. Butters, W. E. Paget and B. Nay, *Synthesis*, 1985, 1155; K. Smith, M. Butters and B. Nay, *Synthesis*, 1985, 1157.

5 V. B. Jigajinni, W. E. Paget and K. Smith, *J. Chem. Res.* (*S*), 1981, 376.

6 M. Hojo and R. Masuda, *Synth. Commun.*, 1975, **5**, 169.

7 *Solid Supports and Catalysts in Organic Synthesis*, ed. K. Smith, Ellis Horwood, Chichester, 1992; *Introduction to Zeolite Science and Practice*, ed. H. van Bekkum, E. M. Flanigan and J. C. Jansen, Elsevier, Amsterdam, 1991.

8 A. P. Singh, S. B. Kumar, A. Paul and A. Raj, *J. Catal.*, 1994, **147**, 360; A. P. Singh and S. B. Kumar, *Appl. Catal. A*, 1995, **126**, 27.

9 L. Delaude and P. Laszlo, *J. Org. Chem*., 1990, **55**, 5260; D. Antenucci, L. Delaude, A.-M. Fransolet and P. Laszlo, *J. Catal*., 1992, **135**, 92.

10 N. Berman and A. J. Lowy, *J. Am. Chem. Soc.*, 1938, **60**, 2596.

11 C. Reichardt, *Solvent Effects in Organic Chemistry*, *Monographs in Modern Chemistry No. 3*, Verlag Chemie, Weinheim, New York, 1979, p. 270.

12 M. J. Mintz and C. Walling, *Org. Synth.*, 1963, **49**, 9.

13 Details can be found in reference 5.

14 A. Zwierzak and A. Koziara, *Tetrahedron*, 1970, **26**, 3521.

15 G. H. Coleman, *J. Am. Chem. Soc.*, 1933, **55**, 3001.

16 *Vogel's Textbook of Practical Organic Chemistry*, 5th edn., Longman, London, 1989, pp. 395–413.

17 A. McKillop, J. C. Fioud and R. P. Hug, *Tetrahedron*, 1974, **30**, 1379.

18 *Handbook of Chemistry and Physics*, 60th edn., CRC Press, Boca Raton, Florida, 1980.

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# Selective carbonylation of norbornene in $scCO_2$

## Palladium(II)-catalyzed carbonylation of norbornene in supercritical carbon dioxide

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## Summary

High conversion and selectivity were observed in Pd(II)-catalyzed carbonylation of norbornene in supercritical carbon dioxide when 1 equivalent of $Et_3N$ and 1 mL MeOH were used.

## Introduction

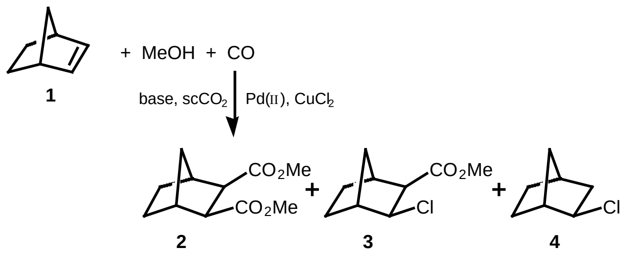
In recent years, the application of supercritical carbon dioxide ($scCO_2$) as a reaction medium for chemical synthesis has received considerable attention.[1] This was enhanced by environmental and health considerations. In addition, $CO_2$ is inexpensive, nontoxic and nonflammable.[2] Furthermore, $CO_2$ separation from a reaction mixture is energy-efficient and the product can be obtained by simple treatment. Owing to the low viscosity of $scCO_2$ and high solubility of gases in $scCO_2$, diffusion of gases and transport of gases across interfaces are much easier in an $scCO_2$ environment than under conventional solution conditions.

Among the large number of studies using transition metals as catalysts in organic synthesis in $scCO_2$, only a few works that employed palladium in $scCO_2$ were reported until very recently.[3–5] It has been shown that using $scCO_2$ as the reaction medium can improve the selectivity of $Co_2(CO)_8$ catalyzed hydroformylation of alkenes.[6–8]

We now report some interesting results obtained from our studies on palladium(II)-catalyzed carbonylation of norbornene in $scCO_2$.

## Results and discussion

When norbornene **1** was carbonylated in the presence of a slight excess of MeOH in $scCO_2$, three products, *cis-exo*-diester **2**, *cis-exo*-β-chloride ester **3** and *exo*-chloronorbornane **4**, were detected (Scheme 1). We found that the conversion was quite good although the selectivity was not ideal. Our observations showed that it was practicable to accomplish carbonylation reactions in $scCO_2$.



**Scheme 1**

Since MeOH is miscible in $scCO_2$,[9] we added an excess of MeOH, which acted as a cosolvent as well as a reactant, to promote the partial dissolution of $CuCl_2$ and $PdCl_2$ in $scCO_2$. When 1 mL MeOH was added, diester **2** was the major product in a yield of 62.4%, together with *exo*-chloronorbornane **4** in a yield of 21.3%. The selectivity to diester was obviously raised, implying that the cosolvent might have improved the selectivity of products. Moreover, raising the reaction temperature resulted in an increase of the yield of **4**. For example, the reaction gave **4** as the major product in 63.4% yield when the temperature was heated to 85°C, while the yield of **2** declined sharply to 21.4% (Table 1).

James and Stille reported that diester **2** and β-chloride ester **3** were obtained in the ratio of 80:17 when palladium(II)-catalyzed carbonylation of norbornene was accomplished in the presence of NaOAc in MeOH solution.[10] The presence of NaOAc might reduce the addition reaction of norbornene and HCl in the reaction system. The carbonylation reaction of norbornene in $scCO_2$ gave expected results in the presence of NaOAc, but we still detected a small amount of *exo*-chloronorbornane **4**. The most satisfactory conversion and selectivity were observed in the reaction using $Et_3N$ as a base and MeOH as a cosolvent. When $Na_2CO_3$ was used, the selectivity of the reaction was not good although the conversion was still satisfactory. This may be attributed to $Et_3N$ which can effectively remove HCl in a homoge-

### Green Context

**The functionalisation of alkenes is one of the most important areas of chemistry, leading from readily available hydrocarbon feedstocks to a range of complex intermediates in only one or two steps. Thus the importance of atom efficient, clean processes in this area is great. This paper details the use of supercritical carbon dioxide as reaction medium in the selective carbonylation of norbornene. The use of palladium catalysts has been difficult in this medium owing to their poor solubility, but the use of methanol improved the efficiency of the reaction significantly, and allowed the direct, one-step synthesis of methyl esters in a highly efficient manner.** ***DJM***

**Table 1** Carbonylation of norbornene under base-free conditions in $scCO_2$[a]

| Run | MeOH/ mL | Cat. | $P_{CO_2}$/ kg cm$^{-2}$ | Reaction Temp./°C | Time/h | Conv. (%) | Yield (%) **2** | **3** | **4** |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.4 | $PdCl_2$ | 13 | 40 | 24 | 99.6 | 27.2 | 21.1 | 36.9 |
| 2 | 0.4 | $PdCl_2$ | 10 | 40 | 12 | 96.7 | 21.6 | 15.6 | 41.4 |
| 3 | 0.4 | $PdCl_2$ | 13 | 50 | 24 | 98.5 | 18.7 | 16.6 | 46.7 |
| 4 | 1 | $PdCl_2$ | 13 | 40 | 24 | 99.8 | 60.5 | 14.1 | 17.0 |
| 5 | 1 | $PdCl_2$ | 13 | 35 | 30 | 98.8 | 62.4 | 6.2 | 21.3 |
| 6 | 1 | $PdCl_2$ | 13 | 33 | 30 | 97.7 | 54.0 | 11.9 | 20.8 |
| 7 | 1 | $PdCl_2$ | 13 | 55 | 24 | 98.1 | 49.5 | 5.8 | 30.7 |
| 8 | 1 | $PdCl_2$ | 13 | 85 | 6 | 100 | 21.4 | 8.1 | 63.4 |
| 9 | 1 | $PdCl_2(PhCN)_2$ | 9 | 40 | 34 | 98.3 | 58.7 | 8.2 | 17.1 |
| 10 | 1 | $PdCl_2(MeCN)_2$ | 14 | 40 | 24 | 97.8 | 57.2 | 6.1 | 22.8 |

[a] Norbornylene (2 mmol), $P_{CO}$ (10 kg cm$^{-2}$), cat. Pd(II) (5.6 mol%), $CuCl_2$ (2 equiv.).

**Table 2** Carbonylation of norbornene under different bases in $scCO_2$[a]

| Run | Cat. | Base[b] | $P_{CO_2}$/ kg cm$^{-2}$ | Reaction Temp./ °C | Time/ h | Conv. (%) | Yield (%) **2** | **3** | **4** | Selectivity (%) [**2**/(**2** + **3** + **4**) × 100%] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $PdCl_2$ | NaOAc | 13 | 40 | 24 | 88.2 | 58.6 | 16.0 | 1.7 | 76.8 |
| 2 | $PdCl_2$ | NaOAc | 12 | 47 | 30 | 99.1 | 77.6 | 16.1 | 0.5 | 82.5 |
| 3 | $PdCl_2$ | $Et_3N$ | 13 | 40 | 30 | 96.1 | 82.2 | 3.4 |  | 96.0 |
| 4[c] | $PdCl_2$ | $Et_3N$ | 13 | 40 | 24 | 91.8 | 73.1 | 1.6 |  | 97.8 |
| 5 | $PdCl_2$ | $Et_3N$ | 13 | 35 | 30 | 94.4 | 82.9 | 3.1 |  | 96.4 |
| 6 | $PdCl_2$ | $Et_3N$ | 17 | 40 | 24 | 100 | 73.5 | 5.9 |  | 82.6 |
| 7 | $PdCl_2$ | $Et_3N$ | 8 | 40 | 24 | 99.0 | 70.0 | 2.8 |  | 96.2 |
| 8 | $PdCl_2(PhCN)_2$ | $Et_3N$ | 8 | 40 | 24 | 99.0 | 75.0 | 5.0 |  | 93.8 |
| 9 | $PdCl_2(PhCN)_2$ | $Et_3N$ | 13 | 40 | 24 | 97.8 | 78.3 | 2.0 |  | 97.5 |
| 10 | $PdCl_2(MeCN)_2$ | $Et_3N$ | 13 | 40 | 24 | 99.8 | 80.0 | 3.9 |  | 95.4 |
| 11 | $PdCl_2(PhCN)_2$ | $Et_3N$ | 13 | 40 | 24 | 98.4 | 80.7 | 2.4 |  | 97.1 |
| 12 | $PdCl_2(MeCN)_2$ | $Na_2CO_3$ | 13 | 40 | 24 | 99.9 | 42.1 | 26.5 | 3.8 | 58.1 |

[a] Norbornene (2 mmol), MeOH (1 mL), cat. Pd(II) (5.6 mol%), $CuCl_2$ (2 equiv.), $P_{CO}$ (10 kg cm$^{-2}$). [b] Base (2 equiv.). [c] $P_{CO}$ (3 kg cm$^{-2}$).

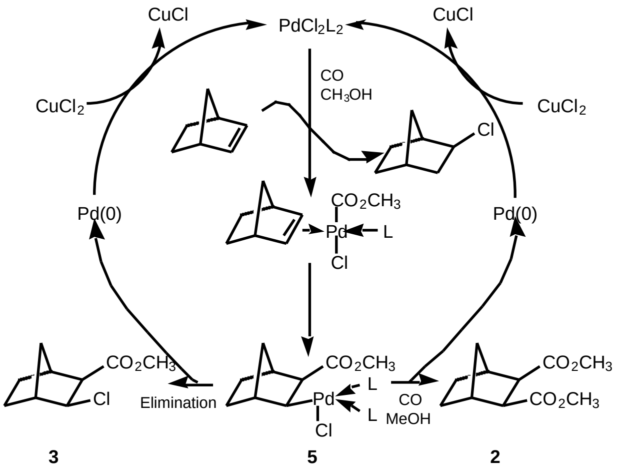
nous fluid, while NaOAc and $Na_2CO_3$ were barely soluble in $scCO_2$ (Table 2).

Three Pd(II) catalysts, $PdCl_2$, $PdCl_2(PhCN)_2$ and $PdCl_2(MeCN)_2$, were investigated under the same reaction conditions and no obvious differences in selectivity and conversion were found.

Excellent results were obtained on the carbonylation of norbornene in $scCO_2$ (about 13 MPa) when bases were present. The yield declined slightly at a much higher (17 MPa) or lower pressure (8 MPa) of $CO_2$. Unlike the significant effect of different amounts of MeOH, changing the pressure of $CO_2$ in our experiment did not have any obvious effect on the selectivity to the diester.

Carroll and Holmes observed that phosphine palladium complexes in $scCO_2$ were insoluble[4] and we may infer that inorganic salts such as $PdCl_2$ or $CuCl_2$ are also insoluble in $scCO_2$. Inorganic salts in MeOH can be soluble. For example, the solubility of $CuCl_2$ is about 37.5 g per 100 g MeOH (20°C). It was reported that MeOH can be soluble in $scCO_2$, therefore an excess of MeOH as cosolvent is favorable for the dissolution of $PdCl_2$ or $CuCl_2$ in $scCO_2$. This suggests that the reaction system might be heterogeneous but the reaction process might be homogeneous.

In all cases, **2** and **3** were produced in different yields, but whether or not **4** was produced depended on the base used. In addition, the ratio of **2** to **3** was also quite sensitive to the base used; triethylamine gave the most satisfactory results. This suggests that the presence of the base might reduce the production of **3** and **4**. The *cis* products showed that the reaction underwent a *cis* insertion of carbomethoxypalladium species to form the σ-bonded complex **5** after initial π-complexation of the olefin to palladium (Scheme 2). Two reaction pathways are available to



**Scheme 2**

complex **5**. Reaction with carbon monoxide and MeOH will afford **2**, or a carbon–palladium–chloride reduction–elimination reaction will form **3**. In the absence of base, HCl produced in the reaction system may react with **1** to form addition product **4**. HCl can be removed by $Et_3N$ effectively, therefore **4** was not detected as $Et_3N$ was used.

In conclusion, carbonylation of norbornene can be successfully carried out in $scCO_2$ using Pd(II) catalysts. The best selectivity was achieved in $scCO_2$ when $Et_3N$ was used as base and MeOH as cosolvent. This work is the first report of a palladium(II)-catalyzed carbonylation reaction in $scCO_2$. Owing to the outstanding advantages of supercritical carbon dioxide, it is believed that organic reactions in $scCO_2$ will receive more and more attention.

## Experimental

### General procedure for carbonylation of norbornene in $scCO_2$

A mixture consisting of norbornene (2 mmol), MeOH (0.4 or 1 mL), base (0 or 4 mmol), Pd(II) catalyst (0.112 mmol) and $CuCl_2$ (4 mmol) was placed in a HF-25 autoclave. CO was pressurized and then liquid $CO_2$ was transferred into the autoclave to the desired pressure using a cooling pump. Then the autoclave was put into an oil-bath under magnetic stirring for the desired reaction temperature and reaction time. After the reaction, the autoclave was allowed to cool to −30 °C in a cooler. The $CO_2$ was vented and the surplus was extracted with *n*-hexane. The extract was filtered and condensed under reduced pressure. The product was analyzed using GC (quantitative analysis) and GC-MS (identification of products).

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## References

1 P. G. Jessop, T. Ikariya and R. Noyori, *Science*, 1995, **269**, 1065.
2 For discussions of the advantages of $scCO_2$, see (*a*) T. Clifford and K. Bartel, *Chem. Ind.*, 1996, 449; (*b*) M. Poliakoff and S. Howdle, *Chem. Ber.*, 1995, **31**, 118; (*c*) H. Black, *Environ. Sci. Technol.* , 1996, **30**, 124A.
3 M. G. Hitzler and M. Poliakoff, *Chem. Commun.*, 1997, 1667.
4 M. A. Carroll and A. B. Holmes, *Chem. Commun.* 1998, 1395.
5 D. K. Morita, D. R. Pesiri, S. A. David, W. H. Glaze and W. Tumas, *Chem. Commun.*, 1998, 1397.
6 J. W. Rathke, R. J. Klinger and T. R. Krause, *Organometallics*, 1991, **10**, 1350.
7 R. J. Klinger and J. W. Rathke, *J. Am. Chem. Soc.*, 1994, **116**, 4772.
8 J. W. Rathke, R. J. Klinger and T. R. Krause, *Organometallics*, 1992, **11**, 585.
9 A. Francis, *J. Phys. Chem.*, 1954, **58**, 1099.
10 D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, 1976, **98**, 1810.

*Paper 9/01396B*

# Triphasic catalyst systems based on surfactant/clay composites

## Facile synthesis of cyano, thiocyano and hydroxy compounds using a triphasic catalyst

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## Summary

Benzyl halides undergo cyanation, thiocyanation and hydroxylation reactions under the influence of triphasic catalysts. The utility of a variety of surfactants, namely cetyltrimethyl-, tetrabutyl-, tetraethyl- and tetramethylammonium chlorides, pillared clays and 18-crown-6 intercalated clay has been demonstrated in these nucleophilic substitution reactions. Furthermore, we noticed that these clay-catalysed reactions are insensitive towards the size of the surfactants used.

## Introduction

Cation-exchanged montmorillonites, clay-supported reagents and pillared clays find extensive applications in organic synthesis under milder reaction conditions.[1–6] These modified clay materials, unlike other conventional catalysts, enjoy considerable advantages such as ease of handling, recyclability, low cost, and easier modulation of acidity levels by suitable exchange of cations thus contributing to the main theme of ‘Green Chemistry’. Our interest in modified clay materials and their applications in organic functional group transformations,[6] prompted us to explore the preparation of benzyl cyanides, thiocyanides and alcohols by employing triphasic catalysts.

Several organic polymers[7–12] or inorganic solid supports[13–16] that contain immobilized organocations such as quaternary ammonium ions have been used as triphasic catalysts.[17] These inorganic solid supports, including clays,[14,15] zeolites[16] and metal oxides,[13] have been used in place of polymers but they generally suffer from disadvantages of low reactivity or structural instability under sustained reaction conditions. Though similar catalytic reactivities can be expected from organic-functionalized silica and alumina, they require relatively elaborate preparative procedures involving the use of silane coupling agents that covalently bind the onium ion to the oxide surface. In contrast, organo-clay assemblies may be readily prepared and enjoy improved catalytic longevity. Thus, clay-based new materials for improved triphasic catalysis are desirable.

The earlier significant contribution of Cornelius and Laszlo entailed the utilization of a commercially available quaternary ammonium montmorillonite (Thixogel VP, a product from Sud-Chemie/AG) to catalyze the formation of symmetrical formaldehyde acetals from organic *gem*-dihalides and alcohols.[14] Almost any organo-clay entity may be expected to function as a triphasic catalyst because of the general hydrophobicity of these materials and their ability to bind ion pairs. In our case, organo-clays form thin membrane-like assemblies at the interface of a hexane-in-water emulsion. Emulsion formation by certain quaternary ammonium clays has been recognized previously in the use of these materials as oil well drilling fluids,[18] but little is known concerning the mechanism. Lin and Pinnavaia have studied the cyanation of 1-bromopentane employing several quaternary ammonium ion exchange forms of hectorite as a triphasic catalyst.[19]

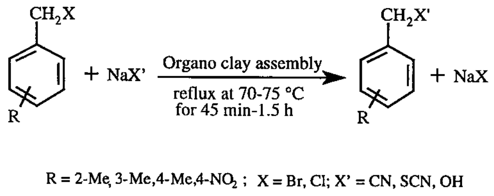
## Results and discussion

We have prepared modified clays by introducing 3-aminopropyltriethoxysilane[6a] and also surfactants[6b] into the clay interlayer and have used these materials in some useful organic transformations. The efficiency of surfactant-pillared clays to act as a dispersed solid phase in a triphasic catalyst system[19] prompted us to study other practically useful reactions using organo-clay assemblies. Herein, we report that benzyl cyanides, thiocyanides and alcohols are easily accessible from the corresponding benzyl halides and sodium cyanide, thiocyanide and hydroxide respectively (Scheme 1). The recovered mass balance is > 90%.

In a control experiment, using only reactants in the absence of catalyst, the reaction is found to be very slow and also results in the generation of a large number of byproducts (Table 1, entry 9). In another experiment, benzyl bromide is found to produce a number of white polymeric byproducts[2b] (entry 10) when natural montmorillonite K10 clay is used. In our initial explorations, the reaction rate at room temperature is found to be very slow but could be accelerated meaningfully under refluxing conditions.

### Green Context

**Benzylic halides can be converted to a range of synthetically useful derivatives by the use of triphasic catalytic systems based on surfactant/clay composites. Catalytic activity seems to be related to the formation of an emulsion, which stably disperses the catalysts.** ***DJM***



**Scheme 1**

The reaction does not occur in the absence of the catalyst. For each reaction system described in Table 1, the organo-clay assembly formed a thin membrane like film at the interface of a hexane-in-water emulsion. However, in the case of unmodified montmorillonite K10 clay, neither the emulsion formation nor any catalytic activity is observed. When only the pillaring solution is used and the experiment is performed in a biphasic catalysis, the conversion is more efficient, an observation corroborated by earlier work.[19] Such a decrease in catalytic efficiency upon onium ion immobilization is a general feature of triphasic catalysis. Next, we set out to analyse the effect of the surfactant's size on the catalytic effectiveness of these reactions. The conversion efficiency essentially remains unchanged as a result of these changes indicating the relative insensitivity of the reaction towards the surfactant size. Although the approach has been explored earlier,[19] we have employed much smaller and more symmetrical surfactants (TBAC, TEAC and TMAC) wherein the generality of the reaction is established with relatively inexpensive and less lachrymatory substrates such as benzyl chlorides rather than bromides.[19] Interestingly, the catalyst can be reused without loss of activity; we have reused the recovered clay twice with reproducible results (entries 32 and 33, Table 1).

In the case of a substrate bearing an electron-withdrawing group, the reaction proceeds expeditiously with rapid consumption of the starting material. However, the reaction invariably leads to the formation of complex byproducts that are devoid of the desired cyanated material according to GC-MS analysis (Hewlett-Packard model 5890 gas chromatograph with a mass spectrometer).

The ability of crown ethers and cryptands to intercalate in smectites is well known.[20] They form very stable polydentate

**Table 1** Preparation of benzyl cyanides, thiocyanides and alcohols from benzyl halides using organo-clay assemblies as triphasic catalysts[a]

| | | | | Product yield (%) | |
|---|---|---|---|---|---|
| Entry | Catalyst | Substrates | | $RC_6H_4CH_2X'$ | Others |
| 1 | TMAC-pillared | $C_6H_5CH_2Br$ | NaCN | 86 | — |
| 2 | TMAC-pillared | $2\text{-}MeC_6H_4CH_2Br$ | NaCN | 84 | — |
| 3 | TMAC-pillared | $3\text{-}MeC_6H_4CH_2Br$ | NaCN | 80 | — |
| 4 | TMAC-pillared | $4\text{-}MeC_6H_4CH_2Br$ | NaCN | 89 | — |
| 5 | TMAC-pillared | $C_6H_5CH_2Br$ | NaSCN | 89 | — |
| 6 | TMAC-pillared | $2\text{-}MeC_6H_4CH_2Br$ | NaSCN | 87 | — |
| 7 | TMAC-pillared | $3\text{-}MeC_6H_4CH_2Br$ | NaSCN | 83 | — |
| 8 | TMAC-pillared | $4\text{-}MeC_6H_4CH_2Br$ | NaSCN | 89 | — |
| 9 | —[b] | $C_6H_5CH_2Cl$ | NaCN | 13 | 40 |
| 10 | K10-montmorillonite clay | $C_6H_5CH_2Cl$ | NaCN | 13 | 41 |
| 11 | Pillaring solution[c] | $C_6H_5CH_2Cl$ | NaCN | 85 | 8 |
| 12 | CTAC-pillared | $C_6H_5CH_2Cl$ | NaCN | 82 | — |
| 13 | CTAC-pillared[d] | $C_6H_5CH_2Cl$ | NaCN | 15 | — |
| 14 | TBAC-pillared | $C_6H_5CH_2Cl$ | NaCN | 79 | — |
| 15 | TEAC-pillared | $C_6H_5CH_2Cl$ | NaCN | 79 | — |
| 16 | TMAC-pillared | $C_6H_5CH_2Cl$ | NaCN | 80 | — |
| 17 | CTAC-pillared[e] | $C_6H_5CH_2Cl$ | NaCN | 79 | — |
| 18 | CTAC-pillared[f] | $C_6H_5CH_2Cl$ | NaCN | 80 | — |
| 19 | 18-Crown-6-clay | $C_6H_5CH_2Cl$ | NaCN | 87 | — |
| 20 | 18-Crown-6 solution[g] | $C_6H_5CH_2Cl$ | NaCN | 95 | — |
| 21 | CTAC-pillared | $C_6H_5CH_2Cl$ | NaOH | 89 | — |
| 22 | TBAC-pillared | $C_6H_5CH_2Cl$ | NaOH | 84 | — |
| 23 | TEAC-pillared | $C_6H_5CH_2Cl$ | NaOH | 79 | — |
| 24 | TMAC-pillared | $C_6H_5CH_2Cl$ | NaOH | 77 | — |
| 25 | TMAC-pillared | $C_6H_5CH_2Br$ | NaOH | 84 | — |
| 26 | TMAC-pillared | $2\text{-}MeC_6H_4CH_2Br$ | NaOH | 84 | — |
| 27 | TMAC-pillared | $3\text{-}MeC_6H_4CH_2Br$ | NaOH | 80 | — |
| 28 | TMAC-pillared | $4\text{-}MeC_6H_4CH_2Br$ | NaOH | 89 | — |
| 29 | 18-Crown-6-clay | $C_6H_5CH_2Cl$ | NaOH | 89 | — |
| 30 | TMAC-pillared | $4\text{-}NO_2C_6H_4CH_2Cl$ | NaCN | Complex product formation | — |
| 31 | TMAC-pillared | $4\text{-}NO_2C_6H_4CH_2Br$ | NaCN | Complex product formation | — |
| 32 | TMAC-pillared[h] | $C_6H_5CH_2Cl$ | NaCN | 80 | — |
| 33 | TMAC-pillared[h] | $C_6H_5CH_2Cl$ | NaCN | 80 | — |

[a] Reaction time 45 min under refluxing conditions except *m*-methylbenzyl halides (1.5 h). [b] Blank experiment. [c] 0.1 ml of 0.15 M pillaring solution (CTAC). [d] Room temperature, 7 h. [e] CTAC-pillared (0.05 g) clay. [f] CTAC-pillared (0.2 g) clay. [g] 0.1 ml of 0.1 M solution of 18-crown-6. [h] Recycled clay (used twice).

coordination compounds in the interlayer space, replacing water molecules which belong to the hydration sphere of the exchangeable cations. Consequently, we decided to conduct the reaction by substituting 18-crown-6 in place of surfactants in the organo-clay assembly. The reaction turned out to be equally facile with this crown ether–clay material.

In summary, the efficiency of triphasic catalysts in the facile syntheses of benzyl cyanides, thiocyanides and alcohols is demonstrated. This method provides a relatively benign approach to the preparation of a variety of benzyl derivatives using a triphasic catalyst. The utility of an 18-crown-6 intercalated clay assembly in these nucleophilic substitution reactions provides relatively improved yields.

## Experimental

Benzyl halides, other chemicals (Acros Organics) and montmorillonite K10 clay (Aldrich) were used as received. Surfactant pillared clay materials were prepared by stirring the sodium-exchanged clay (6 g) in 0.15 M solution of the corresponding surfactants for 100 h at 53 °C.[6b] The solution was filtered, washed repeatedly with distilled water and dried overnight in an oven. X-Ray diffraction data show that the spatial distance in the 001 plane increases from 9 to 16 Å and FT-IR spectra show characteristic stretching frequencies of long chain alkyl groups. The crown ether 'doped' clay assembly was prepared by stirring the sodium exchanged clay (6 g) with an aqueous solution of the potassium salt of 18-crown-6 which, in turn, was prepared by mixing equimolar amounts (0.15 M) of 18-crown-6 with KCl. The reaction mixture was stirred for 50 h at 55 °C, the clay solid was filtered, and washed repeatedly with distilled water to remove any surface-adsorbed crown ether.

### General procedure

In a typical experiment, benzyl chloride (253 mg, 2 mmol) in 7 ml of hexane and sodium cyanide (98 mg, 2 mmol) in 7 ml of distilled water were placed in a round bottomed flask. To this solution, organo-clay (100 mg) was added with stirring for 0.7–1.5 h at 70–75 °C. After completion of the reaction, followed by TLC using hexane as solvent, the product was extracted into dichloromethane, the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford benzyl cyanide (≈90%).

The percentage conversion (entries 9–11 in Table 1) was obtained by analyzing the reaction mixture in a Shimadzu LC-8A modular HPLC system (reversed phase column (ODS), UV detector at 258 nm) using 70% aqueous methanol as the mobile phase. The structural integrity of the products was confirmed by comparing the IR spectra (Perkin-Elmer model 577) and NMR spectra (Perkin Elmer 90 MHz) with those of authentic samples.

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## References

1 (*a*) T. J. Pinnavaia, *Science*, 1983, **220**, 4595; (*b*) P. Laszlo, *Science*, 1987, **235**, 1473; (*c*) J. H. Clark and D. J. Macquarrie, *Chem. Commun.*, 1998, 853.

2 (*a*) J. M. Adams, S. E. Davies, S. H. Graham and J. M. Thomas, *J. Catal*., 1982, **78**, 197; (*b*) J. A. Ballantine, J. H. Purnell and J. M. Thomas, *Clay Miner.*, 1983, **18**, 347.

3 (*a*) J. A. Ballantine, M. Davies, H. Purnell, M. Rayanakorn, J. M. Thomas and K. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1981, 8; (*b*) R. Burch and C. I. Warburton, *J. Catal*., 1986, **97**, 511; (*c*) O. Sieskind and P. Albrecht, *Tetrahedron Lett*., 1985, **26**, 2135.

4 J. Tateiwa, H. Horiuchi, K. Hashimoto, T. Yamauchi and S. Uemura, *J. Org. Chem*., 1994, **59**, 5901.

5 J. Cabral, P. Laszlo and M. T. Montaufier, *Tetrahedron Lett*., 1988, **29**, 547.

6 (*a*) P. Kannan, K. Pitchumani, S. Rajagopal and C. Srinivasan, *Chem. Commun*., 1996, 369; (*b*) P. Kannan and K. Pitchumani, *Catal. Lett*., 1997, **45**, 271; (*c*) P. Kannan, K. Pitchumani, S. Rajagopal and C. Srinivasan, *J. Mol. Catal*., 1997, **118**, 189; (*d*) R. S. Varma and K. P. Naicker, *Tetrahedron Lett*., 1998, **39**, 2915; (*e*) R. S. Varma and D. Kumar, *Catal. Lett*., 1998, **53**, 225; (*f*) R. S. Varma, K. P. Naicker and P. J. Liesen, *Tetrahedron Lett*., 1998, **39**, 3977.

7 S. L. Regen, *J. Am. Chem. Soc.*, 1975, **97**, 5956.

8 S. L. Regen, *Nouv. J. Chem*., 1982, 629.

9 (*a*) M. Tomoi and W. T. Ford, *J. Am. Chem. Soc*., 1981, **103**, 3821; (*b*) M. Tomoi and W. T. Ford, *J. Am. Chem. Soc*., 1981, **103**, 3828.

10 F. Montanari and P. Tundo, *J. Org. Chem*., 1981, **46**, 2125.

11 Y. Kimura and S. L. Regen, *J. Org. Chem*., 1983, **48**, 195.

12 M. Tomoi, *J. Polym. Sci., Polym. Chem. Ed.*, 1985, **23**, 49.

13 (a) P. Venturello, P. Tundo and E. Angeletti, *J. Am. Chem. Soc*., 1982, **104**, 6547; (b) P. Venturello, P. Tundo and E. Angeletti, *J. Am. Chem. Soc*., 1982, **104**, 6551.

14 A. Cornelius and P. Laszlo, *Synthesis*, 1982, 162.

15 A. Kadkhodayan and T. J. Pinnavaia, *J. Mol. Catal*., 1983, **21**, 109.

16 P. Tundo, P. Venturello and E. Angeletti, *Isr. J. Chem*., 1985, **26**, 283.

17 F. Rolla, W. Roth and L. Horner, *Naturwissenschaften*, 1977, **64**, 337.

18 G. R. Gray, *Composition and Properties of Oil Well Drill Fluids*, 4th edn., Gulf: Houston, 1980, p. 323.

19 C. L. Lin and T. J. Pinnavaia, *Chem. Mater*., 1991, **3**, 213.

20 E. Ruiz-Hitzky and B. Casal, in *Chemical Reactions in Organic and Inorganic Constrained Systems*, ed. R. Setton, *NATO ASI Ser., Ser. C*, 1986, p. 179.

*Paper 8/07092J*

# Biocatalysis

## Preparation and functionalization of N-heterocycles

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### Summary

Biocatalysis has proven to be a useful supplementary technology for the chemical industry, allowing in some cases reactions which are not easily conducted by classical organic chemistry or in other cases allowing reactions which can replace several chemical steps. Highly chemo-, regio- and stereoselective bioconversions can simplify manufacturing processes to make them even more economically attractive and environmentally acceptable. The examples described are a selection of biocatalytic processes used for the preparation or modification of *N*-heterocycles.

### Introduction

Aromatic and aliphatic N-heterocycles are frequent structural motifs in nature's molecules and in man-made chemical active substances such as pharmaceuticals and agrochemicals. Nature's synthesis of amino acids, ribonucleosides, vitamins and the broad spectrum of biologically relevant compounds contrasts with the synthetic methods used by man. Efficient catalysis by enzymes results in highly selective reactions under mild conditions. However, the rules dictated by economics give the highest scores to technologies leading to cheap processes. Fortunately, processes generating less environmental damage are increasingly better financially rewarded due to the increasing costs of by-product and solvent disposal.

Organic chemistry and other manufacturing technologies are very innovative to further increase the environmental compatibility of chemical production technologies. During the past two decades biocatalysis has also proven to be a useful supplementary technology, allowing in some cases reactions which are not easily conducted by classical organic chemistry or in other cases allowing reactions which can replace several chemical steps. Highly chemo-, regio- and stereoselective bioconversions can simplify manufacturing processes to make them even more economically attractive and environmentally acceptable.

This article can not give a complete listing on all the different N-heterocyclic compounds produced by biocatalysis. It focuses on biocatalytic processes that are presently used as chemoenzymatic or entirely fermentative processes for the preparation of N-heterocycles to give examples of the broad applicability of biocatalysis today.

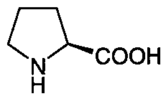
### 1 *De novo* synthesis of N-heterocyclic compounds

The isolation of substituted N-heterocycles from plants or other natural raw materials, as well as the production by micro-organisms grown on renewable resources such as glucose, are in principle ecologically very favorable manufacturing methods. The biosynthetic capabilities of living entities have found many commercial applications for the production of a wide variety of N-heterocycles. These processes have been reviewed by many authors in detail and therefore only a brief summary will be given in this article with references to recent publications.

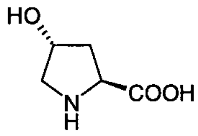
*N*-Heterocycles are found in different classes of valuable natural compounds like amino acids, nucleosides, vitamins, and alkaloids. In many cases the desired substance is available from cheap natural raw materials by direct isolation. If the content is too low or no cheap raw material is available, complex biomolecules can be produced by fermentation. Several of the described compounds are produced by chemical, chemo-enzymatic or fermentative processes or isolated from natural sources simultaneously by different companies.

#### L-Proline and hydroxy-L-proline

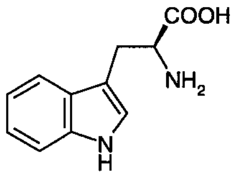
For L-proline (**1**) and *trans*-4-hydroxy-L-proline (**2**) (as well as cystine and tyrosine), isolation from collagen is still the most economical production method. The standard procedure for isolating an amino acid from an aqueous protein hydrolysate is chromatography on strong acidic ion-exchange resins. Even pharmaceutical grade amino acids are obtained by this procedure.[1] For the fermentative production of L-proline, micro-organisms of the genera *Brevibacterium, Corynebacterium* and *Serratia* have been used. Mutants of *Brevibacterium flavum* requiring isoleucine for



L-proline (**1**)



*trans*-4-hydroxy-L-proline (**2**)



L-tryptophan (**3**)

### Green Context

**Many N-heterocycles are produced by nature, and are of interest due to their bio-activity. The use of biotechnology in their synthesis has been successfully applied to a range of these molecules. This review details syntheses of N-heterocycles from non-heterocyclic starting materials, and others involving modification of the ring structure. Many of these transformations represent useful extensions of the classical chemical routes, often with significantly improved environmental impacts. While many syntheses are impressive, effort is still required to push up product concentrations in the final fermentation solution.** ***DJM***

growth, and which are resistant to certain amino acid analogs, are capable of producing up to 40 g L$^{-1}$ of L-proline.[2]

### L-Tryptophan

Pathway engineering was performed in *Corynebacterium glutamicum* using molecular biological techniques to increase the production of L-tryptophan (**3**) up to 43 g L$^{-1}$.[3] However, this amino acid is currently prepared with chemo-enzymatic methods discussed in a later section of the article.

### Ribonucleosides

Japanese companies have developed very efficient fermentation methods for the production of the ribonucleosides adenosine (**4**), guanosine (**5**), uridine (**6**), cytidine (**7**) and inosine (**8**). With the exception of inosine the ribonucleosides can also be prepared from polymeric ribonucleosides (RNA) isolated from yeast cells. Inosine 5′-monophosphate (IMP) and guanosine 5′-monophosphate (GMP) are important purine nucleosides with flavor-enhancing activity. Both IMP and GMP are produced on a multiton per year scale.

Table 1 gives examples of biocatalysts developed for the preparation of ribonucleosides. With respect to ribonucleosides it is interesting to point out that presently no fermentation methods have been developed for the preparation of 2′-deoxyribonucleosides. The classical source for 2′-deoxyribonucleosides is hydrolyzed salmon sperm DNA.

**Table 1** Microbial strains developed for the production of ribonucleosides

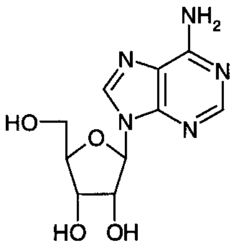
| Ribonucleoside | Product conc. /g L$^{-1}$ | Microorganism | Ref. |
|---|---|---|---|
| Adenosine | 16 | *Bacillus subtilis* | 4 |
| Cytidine | 19 | *Bacillus subtilis* | 5 |
| Guanosine | 20 | *Bacillus subtilis* | 6 |
| Inosine | 31 | *Corynebacterium ammoniagenes* | 7 |
| Uridine | 65 | *Bacillus subtilis* | 8 |

### Riboflavin

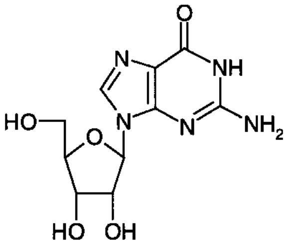
Vitamin B$_2$ (riboflavin) (**9**) is produced on a large scale by chemical synthesis or by a combined fermentative/chemical process. In recent years, novel microbiological production processes for the synthesis of riboflavin have been developed, some of which represent attractive alternatives to the current chemical production processes. BASF (Germany) uses the genetically modified fungus *Ashbya gossypii*[9] and Hoffmann-La Roche (Switzerland) a recombinant *Bacillus subtilis* strain. The product concentrations for both strains are over 10 g L$^{-1}$. van Loon *et al.* have shown that the fermentation process offers significant environmental and economic advantages primarily because it uses predominantly natural renewable raw materials.[10]

### Cobalamin (vitamin B$_{12}$)

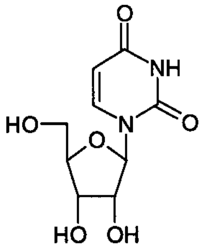
The chemical synthesis of cobyrinic acid (**10**), the core heterocycle of cobalamin, was the biggest project in organic synthesis until today. The groups of Woodward in Havard and Eschenmoser in Zürich joined forces to prepare cobyrinic acid in 57 chemical steps from 1960 to 1972.[11,12] This precludes chemical production. In the past cobalamin was isolated from residues of antibiotic fermentations.[13] Today it is exclusively produced by fermentation. *Propionibacteria* and *Pseudomonada*[14–16] are frequently used and they produce >150 mg L$^{-1}$ of cobalamin inside the cells.



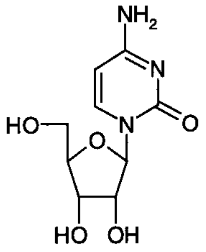
Adenosine (**4**)



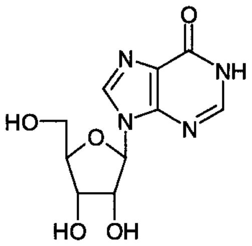
Guanosine (**5**)



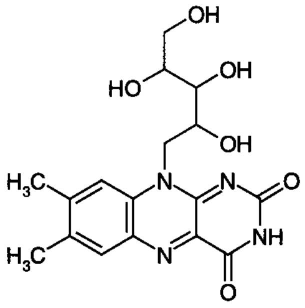
Uridine (**6**)



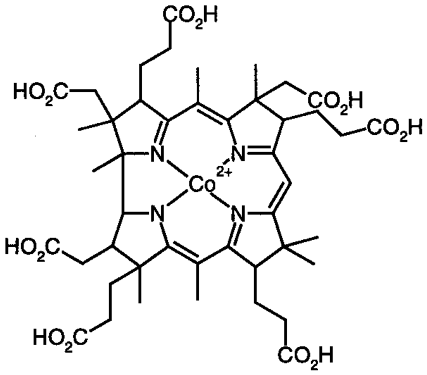
Cytidine (**7**)



Inosine (**8**)



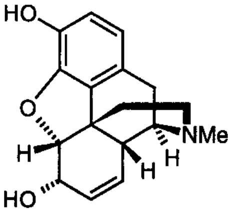
Riboflavin (**9**)



Cobyrinic acid (**10**)

### Morphine

One of the most notable isoquinoline alkaloids is morphine (**11**) which is also the major alkaloid of opium produced from the plant *Papaver somniferum*. It is still the most effective painkiller available in medical practice. At the same time, it is addictive, and the mis-use of the diacetate, heroin, as a narcotic and euphoric drug can lead to the early death of the addict. The lethal dose in humans lies between 1 and 10 mg.

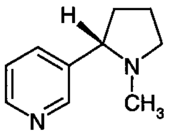


Morphine (**11**)

A review on the chemistry and biology of isoquinoline alkaloids has been published by Phillipson *et al.*[17]

### Nicotine

Dried leaves of the tobacco plants *Nicotiana rustica* and *N. tabacum* contain as much as 2–8% of enantiopure (*S*)-nicotine (**12**). When grown on fertile soils under irrigation for a period of several years, *N. rustica* can produce consistently 16.5 kg per 1000 $m^2$. Surprisingly, this natural alkaloid has not been seriously considered as a potential renewable resource and text books on this topic generally lack references to (*S*)-nicotine. The only large scale application of nicotine is its use as an insecticide. Before the first synthetic insecticides came to the market approximately 2800 tons of (*S*)-nicotine per year were used as a crop protectant. The lack of any specific applications for nicotine as a renewable chemical may be because nicotine is very toxic, and the selective functionalization of nicotine at the pyridine or the pyrrolidine ring is difficult to control by chemical means. This restricts the chemical preparation of semi-synthetic pyridines using nicotine as a starting material.[18] Recently, selective biological oxidations were applied to prepare a series of nicotine analogues (see below).



(*S*)-Nicotine (**12**)

### Secondary metabolites

The fermentative production of secondary metabolites is a very important business. The scope of compounds manufactured by *de novo* biosynthesis is also extremely broad. As also mentioned previously, a detailed description of *N*-heterocycles produced in this manner is beyond the scope of this article.

β-Lactam antibiotics are the most prominent class of compounds in the group of secondary metabolites. The total output from approximately 50 producers is estimated to be 10000–20000 tons per year. The bulk price for penicillin G is 25–30 \$/kg.[19]

For the preparation of a wide variety of commercial semi-synthetic antibiotics, the side-chain phenylacetic acid of penicillin G (**13**) and the D-α-aminoadipic acid of cephalosporin C (**14**) are first removed enzymatically to prepare the crucial intermediates 6-aminopenicillanic acid (**15**) and 7-aminocephalosporanic acid (**16**). Both enzymatic processes replace classical chemical routes which were applied for many years to hydrolyse the amide bonds attaching the side chains. The phenylacetic acid is cleaved off the penicillin G with the enzyme Penicillin G amidase.[19,20] 7-Aminocephalosporanic acid is prepared from cephalosporin C by a 3-step, 2-enzyme process. D-Amino acid oxidase deaminates cephalosporin C to give α-ketoadipyl-7-aminocephalosporanic acid which then spontaneously forms glutaryl-7-aminocephalosporanic acid. Glutaryl-7-aminocephalosporanic acid acylase then converts this product to 7-aminocephalosporanic acid. $H_2O_2$ produced by the oxidase reacts in the absence of catalase with the keto acid to glutaryl-7-aminocephalosporanic acid *via* oxidative decarboxylation. Glutaryl-7-aminocephalosporanic acid acylase then converts this product to 7-aminocephalosporanic acid. The yield of glutaryl-7-aminocephalosporanic acid from the first enzymic reaction is approximately 95%; the yield of 7-amino-cephalosporanic acid from the second enzymic reaction is also approximately 95%.[21]

### 'Green' indigo production from glucose in *E. coli*

The production of indigo (**17**) by the fermentation of glucose is an interesting alternative to the production by chemical synthesis. The fermentation strategy of Genencor (USA) is to maximize the shikimic acid pathway followed by channeling this carbon through a mutated tryptophan synthase resulting in the production of indole. Cloned naphthalene dioxygenase is used to convert indole to indoxyl, which is spontaneously air oxidized to indigo.[22] This novel biosynthesis of indigo has, however, so far not been sufficiently economical to replace the present cheap chemical synthesis of indigo.

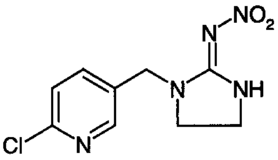
## 2 Bioconversions for the modification of substituted N-heterocycles

A wide variety of chemoenzymatic processes have been developed for the large scale preparation of functionalized heterocycles. Some of these biocatalytic processes were developed using enzymes naturally formed by micro-organisms degrading certain *N*-heterocycles. A review on the microbial metabolism of pyridines, quinoline and acridine was published recently by Kaiser *et al.*[23] Also, hydrolytic enzymes such as esterases, lipases, amidases and nitrile hydratases have been applied to prepare enantiomerically pure cyclic amino acids. The main advantage of most of the biocatalytic processes mentioned in this section is the high selectivity of the reaction which increases the yield compared to chemical routes and simplifies the purification of the desired products. As a consequence such biocatalytic routes are economically and ecologically favorable manufacturing methods.

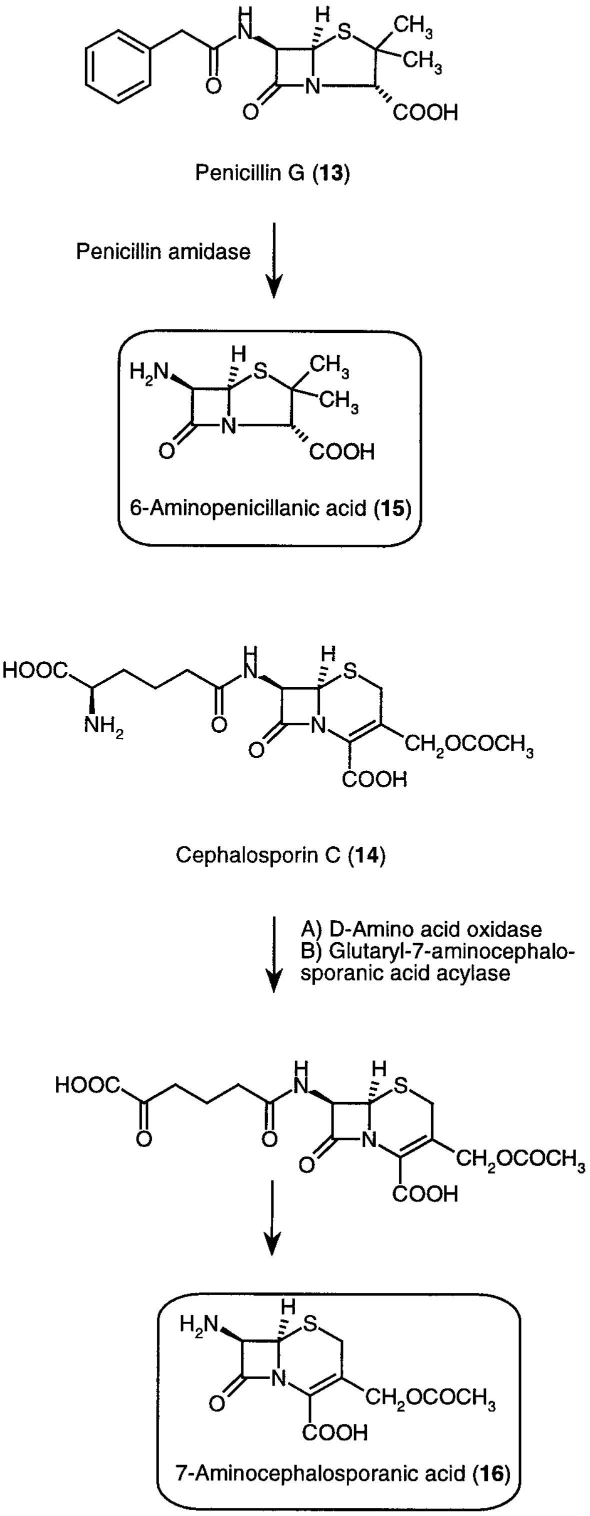
### Biocatalytic ring hydroxylation of aromatic N-heterocycles

The enzymatic hydroxylation of substituted pyridines and pyrazines occurs chemoselectively at the position α to the ring nitrogen. The oxygen for the initial hydroxylation reaction is derived from $H_2O$ instead from $O_2$. In the case of the dehydrogenase forming 6-hydroxynicotinic acid from nicotinic acid it was shown that this membrane bound enzyme system contains a molybdenum cofactor.[24] The volumetric productivity of these hydroxylations is generally very high and wild type cells can be used for these bioconversions (Table 2).

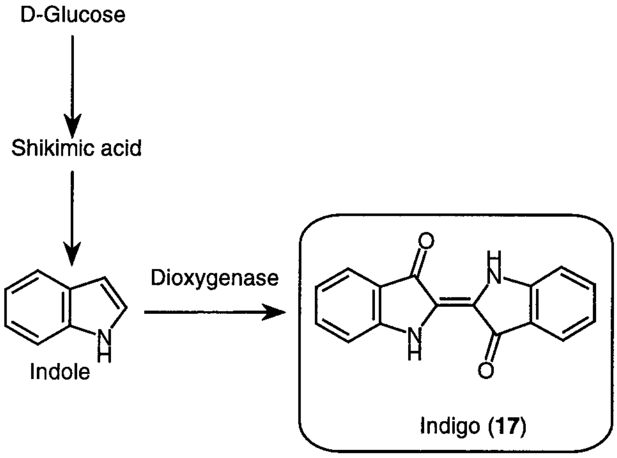
Several biotransformations with 3-substituted pyridines were developed to gain cheap access to building blocks used for the preparation of insecticides such as Imidacloprid™ (**18**) and analogues.[32]



Imidacloprid (**18**)



**Scheme 1**



**Scheme 2**

6-Hydroxy-(*S*)-nicotine (**19**) was used as starting material for the preparation of 5,6-disubstituted nicotine analogues. Although the history of nicotine is well over 100 years old such disubstituted derivatives have not been described before, indicating that bioconversions can give access to novel building blocks. Pyrazinecarboxylic acid formed as an intermediate after the hydrolysis of 2-cyanopyrazine by a nitrilase is regiospecifically hydroxylated to 5-hydroxypyrazinecarboxylic acid (**20**). The chemical syntheses of 5-hydroxy- or 5-chloropyrazinecarboxylic acid are circumstantial.[30]

## Enzymatic oxidation of alkyl groups on N-heterocycles

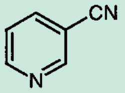
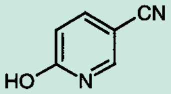
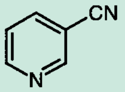
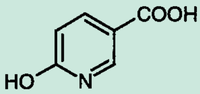
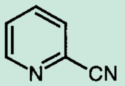
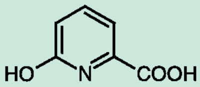
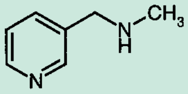
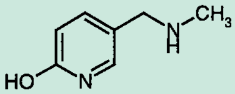
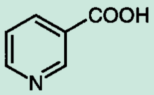
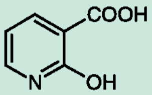
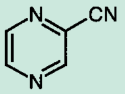
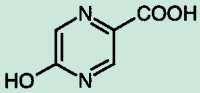
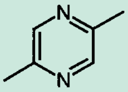
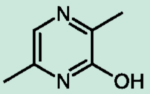
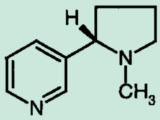
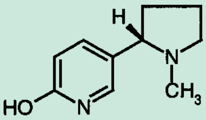
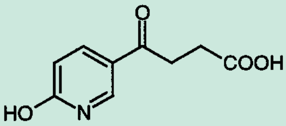
Chemical oxidation reactions used for the industrial-scale preparation of heteroaromatic monocarboxylic acids from heteroaromatic compounds bearing one or more alkyl groups are generally nonspecific, leading to the formation of byproducts. For example, the oxidation of 5-ethyl-2-methylpyridine (**24**) with $HNO_3$ leads to the formation of pyridine-3-carboxylic acid (nicotinic acid). With this process it would not be possible to selectively oxidize the terminal methyl group of the ethyl function without oxidizing the methylene group or the methyl group in position 2. We discovered that micro-organisms grown on xylene as the sole carbon and energy source were capable of selectively oxidizing a single methyl group on heteroarenes. The oxidation of 2,5-dimethylpyrazine (**21**) to 5-methylpyrazine-2-carboxylic acid (**22**) is now performed commercially with wild type micro-organisms *Pseudomonas putida*. The oxidation of 2-chloro-3,6-dimethylpyrazine (**23**) is regiospecific because the substituent in *ortho* position to the methyl group prevents the hydroxylation by monooxygenase.[33]

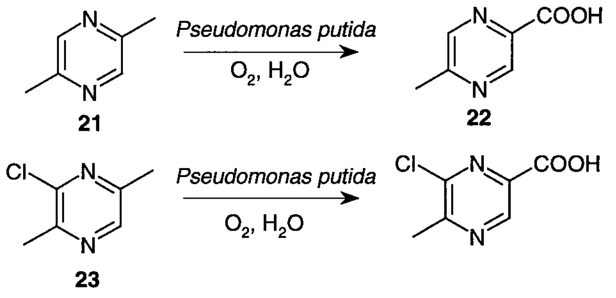
We demonstrated that *Pseudomonas oleovorans* previously grown on *n*-octane catalyzes the oxidation of ethyl groups on heteroaromatic compounds to the corresponding acetic acid derivatives. The oxidation of 5-ethyl-2-methylpyridine (**24**) to 5-methylpyridine-3-acetic acid (**25**) illustrates the selectivity of this reaction very well because no byproducts were detected after the reaction was complete.[34]

## Chemoenzymatic synthesis of L-tryptophan

An alternative process to the *de novo* biosynthesis of L-tryptophan (**3**) is the use of L-tryptophan indole synthase ('tryptophanase') from *Proteus rettgeri*. This micro-organism accumulates this enzymes up to 6% of the total soluble protein. L-Tryptophan is synthesized from indole, pyruvate and ammonia. For the production of tryptophan inosine was added to the reaction mixture. Tryptophan formed an insoluble complex with ino-

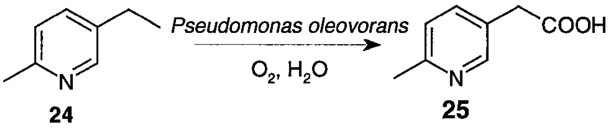
**Table 2** Microbial conversions of substituted pyridines

| Starting material | | Product | Product concentration (enzymes)<br>Biocatalyst |
|---|---|---|---|
|  | → |  | 45 g $L^{-1}$ (Hydroxylase)<br>*Comamonas testosteroni*[25] |
|  | → |  | 40 g $L^{-1}$ (Nitrilase & Hydroxylase)<br>*Agrobacterium* sp.[26] |
|  | → |  | 55 g $L^{-1}$ (Nitrilase & Hydroxylase)<br>*Alcaligenes faecalis*[27] |
|  | → |  | 25 g $L^{-1}$ (Hydroxylase)<br>*Arthrobacter ureafaciens*[28] |
|  | → |  | 6.5 g $L^{-1}$ (Hydroxylase)<br>*Proteobacteria*[29] |
|  | → | <br>**20** | 40 g $L^{-1}$ (Nitrilase & Hydroxylase)<br>*Agrobacterium* sp.[30] |
|  | → |  | 8 g $L^{-1}$ (Hydroxylase)<br>*Rhodococcus erythropolis*[31] |
|  | → | <br>**19** | 30 g $L^{-1}$ (Hydroxylase)<br>*Arthrobacter oxydans*[18] |
| | ↘ |  | 15 g $L^{-1}$ (Several enzymatic steps)<br>*Pseudomonas* sp.[18] |



**Scheme 3**

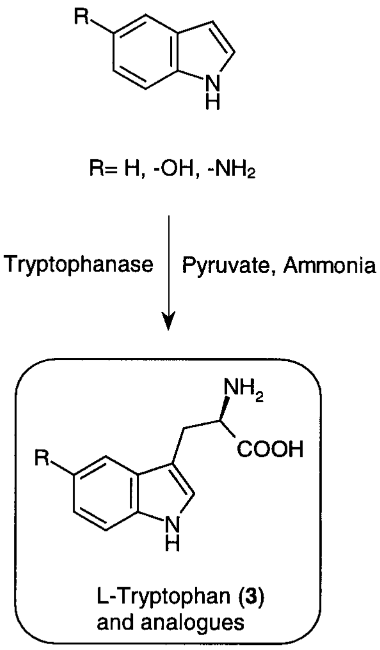
sine and therefore the equilibrium of the reaction was shifted to the product side and in this case up to 100 g $L^{-1}$ of tryptophan was formed.[35] Tryptophanase also accepts 5-aminoindole and 5-hydroxyindole as substrates.



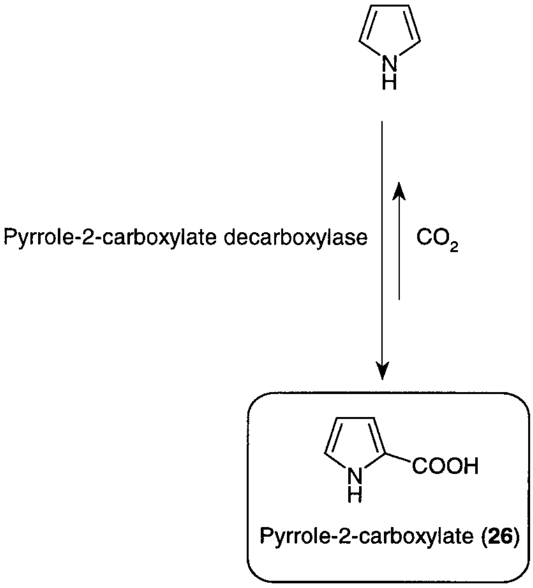
**Scheme 4**

## Microbial synthesis of pyrrole-2-carboxylate

Pyrrole-2-carboxylate (**26**) was synthesized from pyrrole using the carboxylation reaction of the reversible pyrrole-2-carboxylate decarboxylase from *Bacillus megaterium*. By addition of high amounts of bicarbonate, the reaction equilibrium was shifted



**Scheme 5**

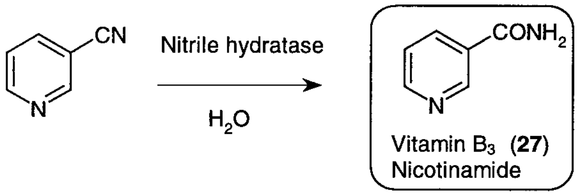


**Scheme 6**

towards pyrrole-2-carboxylate. A unique feature of this enzyme is its requirement for an organic acid, such as acetate, propionate, butyrate or pimelate.[36]

## Vitamin $B_3$ from 3-cyanopyridine

Nicotinamide, or vitamin $B_3$ (**27**), is an essential component of enzymes catalyzing hydrogenation and dehydrogenation reactions. Nicotinamide is also used as a vitamin supplement for food and animal feed. One commercial process for the manufacture of nicotinamide is alkaline hydrolysis of 3-cyanopyridine. The hydrolysis is normally carried out with a catalytic amount of sodium hydroxide. A typical yield of this process is 96%, but nicotinic acid can be up to 4% in the product. An alternative biological method for the hydrolysis of 3-cyanopyridine to nicotinamide involves micro-organisms that produce nitrile hydratase. The use of the bacterial nitrile hydratase formed by *Rhodococcus rhodochrous* J1 for the industrial production of *ca.* 20000 tons of acrylamide per year was developed in Japan.[37] The same biocatalyst can be used for the hydrolysis of 3-cyanopyridine in the form of immobilized cells. The absolute selectivity of the bioconversion is the main advantage over the chemical process. No nicotinic acid is formed as a byproduct. Lonza (Switzerland) has built a plant in China producing *ca.* 3000 tons of nicotinamide per year with this biocatalyst.



**Scheme 7**

## Enantiomerically pure cyclic amino acids

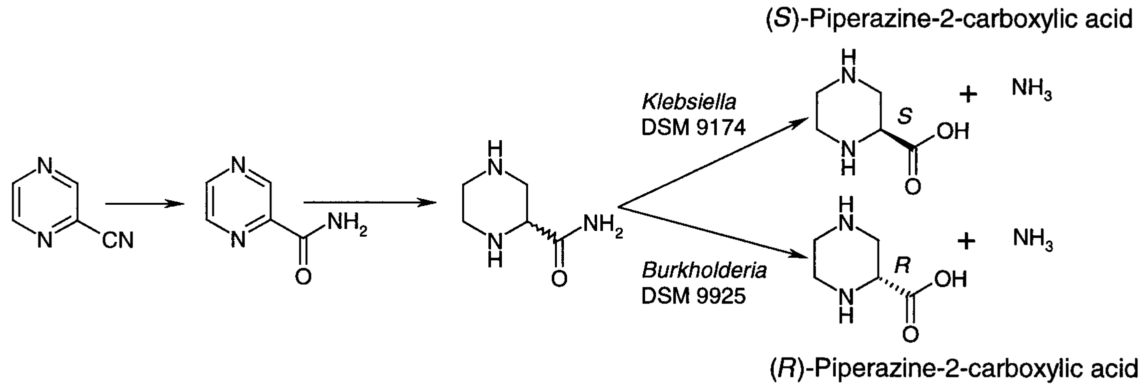
Non-proteinogenic amino acids such as piperidine-2-carboxylic acid (pipecolic acid) (**28**), piperazine-2-carboxylic acid (**29**) and D-proline are precursors of numerous bio-active compounds.

The best chemical route to the pure enantiomers of pipecolic acid and piperazine-2-carboxylic acid is classical resolution of the racemate by fractional crystallization of diastereomeric salts. Asymmetric syntheses for (*S*)-pipecolic acid have been developed as well as a kinetic resolution of (*R*,*S*)-*n*-octylpipecolate using a partially purified *Aspergillus niger* lipase. (*S*)-Piperazine-2-carboxylic acid has also been prepared by kinetic resolution of racemic 4-(*tert*-butoxycarbonyl)piperazine-2-carboxamide with leucine aminopeptidase. Both of these biocatalytical processes have practical disadvantages in that the preparation of the racemic starting materials is complicated and the availability of the biocatalysts for large scale production is limited. Whole cells of wild-type micro-organisms that contain stereospecific amidases have been used for the kinetic resolution of racemic piperazine-2-carboxamide and racemic piperidine-2-carboxamide to the corresponding enantiomerically pure carboxylic acids. These kinetic resolutions are attractive because the starting materials can be easily prepared from 2-cyanopyrazine and 2-cyanopyridine *via* the corresponding aromatic carboxamides. Furthermore, the micro-organisms can be grown in fermenters on the racemic carboxamides at the same time as the biotransformations are taking place.

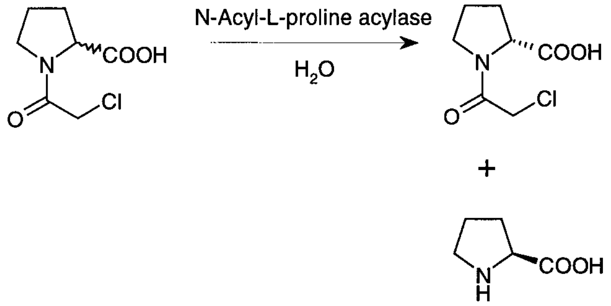
*N*-Acyl-L-proline acylases have been used for the production of *N*-acyl-D-proline and L-proline from racemic *N*-acylproline. The *N*-acyl-L-proline acylase from *Commomonas testosteroni* has a broad substrate specificity and was used for the hydrolysis of *N*-chloroacetyl-derivatives of azetidine-2-carboxylic acid, proline and pipecolic acid.[38]

An analogous biocatalytic process was developed for the production of CBZ-D-proline which can be used directly for subsequent coupling reactions. A further advantage of this process is the high overall yield of the biotransformation since the solubility of CBZ-D-proline is very low in the aqueous broth.[39]

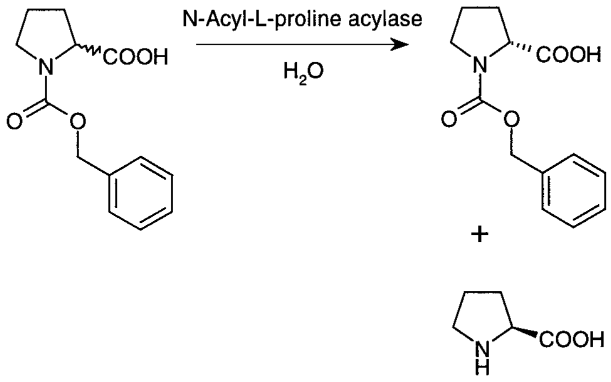
The obvious disadvantage of these kinetic resolutions of racemic D,L-proline derivatives is the low maximal theoretical yield of 50%. A new asymmetric route for the production of D-proline was developed from L-arginine as starting material. In a first chemical step L-arginine was converted to (*S*)-5-[amino-



Scheme 8



Scheme 9

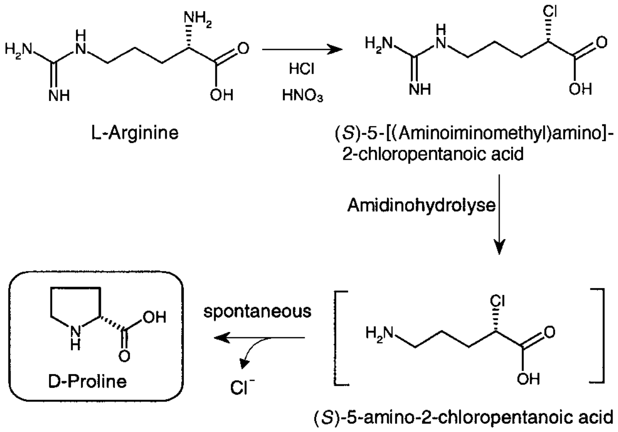


Scheme 10

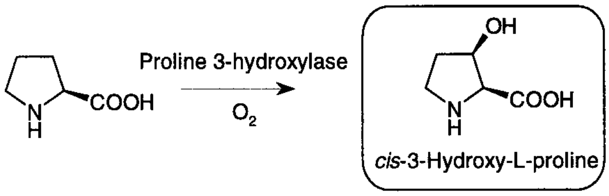
iminomethyl)amino]-2-chloropentanoic acid. This compound was then used to screen for micro-organisms capable of accepting this molecule as a nitrogen source for growth. *Pseudomonas aeruginosa* could convert (*S*)-5-[(aminoiminomethyl)amino]-2-chloropentanoic acid to (*S*)-5-amino-2-chloropentanoic acid, which spontaneously cyclized with inversion of configuration to D-proline.[40]

## Production of non-proteinogenic hydroxyprolines

Among eight isomers of hydroxyproline, only *trans*-4-hydroxy-L-proline is abundant in nature as a component of collagens produced by higher organisms. It is known that procollagen-proline dioxygenase hydroxylates L-proline residues of procollagen post-translationally to *trans*-4-hydroxy-L-proline. Recently a novel enzyme was found capable of hydroxylating free L-proline to *cis*-3-hydroxy-L-proline. The purified enzyme showed properties of a 2-oxoglutarate-dependent dioxygenase.[41]



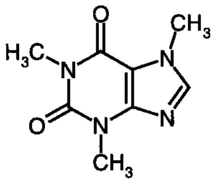
Scheme 11



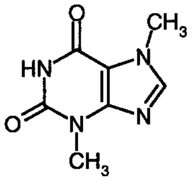
Scheme 12

## Demethylation of caffeine to theobromine

The caffeine content of the bean of *Coffea canephora* (dry basis) is *ca.* 2.0% and is currently a by-product of the manufacture of caffeine-free coffee. Theobromine is the principle alkaloid of cacao beans which contain 1.5–3% of this base.[42] The selective biological demethylation of caffeine to theobromine was achieved by caffeine-degrading bacteria. *Pseudomonas putida* strains can produce nearly 20 g $L^{-1}$ theobromine from caffeine.[43] The presence of zinc ions is necessary to inhibit the further degradation of the accumulating theobromine.



Caffeine



Theobromine

## Conclusions

There are several other N-heterocyclic compounds which can be manufactured by microbial catalysts. The examples described are only a small selection of biocatalytic processes which are presently used for the preparation of N-heterocycles. Due to the advances of molecular biology it may be possible in future to modify the natural producers like plants, animals, microorganisms to produce related but chemically distinct compounds as a renewable raw material basis for the chemical industry.

Biocatalysis has proven to be a useful supplementary technology for the chemical industry, allowing reactions which are not easily conducted by classical organic chemistry. The range of applications is not limited to natural compounds like amino acids, nucleosides, or vitamins. Bioconversions can also be used to perform chemical reactions which are in the domain of classic organic chemistry. The examples of nitrile hydratizing microbial strains used for the production of acrylamide or nicotinamide on an industrial scale show that biocatalysts can compete even with cheap traditional catalysts such as mineral acids and bases.

## References

1 A. Kleemann, W. Leuchtenberger, B. Hoppe and H. Tanner, *Amino Acids*, in *Ullmann's Encyclopedia of Industrial Chemistry*, ed. W. Gerhartz, VCH Verlagsgesellschaft, Weinheim, 1985.
2 F. Yoshinaga, *Prog. Ind. Microbiol.*, 1986, **24**, 117.
3 R. Katsumata and M. Ikeda, *Bio/Technology*, 1993, **11**, 921.
4 K. Haneda, A. Hirano, R. Kodaira and S. Ohuchi, *Agric. Biol. Chem.*, 1971, **35**, 1906.
5 S. Asahi, Y. Tsunemi and M. Doi, *Biosci. Biotechnol. Biochem.*, 1995, **59**, 2123.
6 K. Miyagawa, H. Kimura, K. Nakahama, M. Kikuchi, M. Doi, S. Akiyama and Y. Nakao, *Bio/Technology*, 1986, **4**, 225.
7 H. Mori, A. Iida, T. Fujio and S. Teshiba, *Appl. Microbiol. Biotechnol.*, 1997, **48**, 693.
8 M. Doi, Y. Tsunemi and S. Asahi, *Biosci. Biotechnol. Biochem.*, 1994, **58**, 1608.
9 P. Philippsen, M. Pompejus and H. Seulberger, *WO* 98/29539, 1998.
10 A. P. G. M. van Loon, H.-P. Hohmann, W. Bretzel, M. Hümbelin and M. Pfister, *Chimia*, 1996, **50**, 410.
11 W. Friedrich, *Handbuch der Vitamine*, Urban & Schwarzenberg, Munich, 1987.
12 S. Fukui and S. Shimizu, *Antibiotics, Vitamins and Hormones*, ed. F. Korte and M. Goto, Georg Thieme Verlag, Stuttgart, 1977.
13 C. Spalla, in *Biotechnology of Vitamins, Pigments and Growth Factors*, ed. E. J. Vandame, Elsevier, Amsterdam, 1989.
14 T. Karuhara and I. Nakamura, *Adv. Biochem. Eng. Biotechnol.*, 1984, **29**, 35.
15 H. C. Friedmann and L. M. Cagen, *Annu. Rev. Microbiol.*, 1970, **24**, 159.
16 J. Florent and L. Ninet, in *Microbial Technology*, ed. H. J. Peppler and D. Perlman, Academic Press, New York, 1979.
17 J. D. Phillipson, M. F. Roberts and M. H. Zenk, *The Chemistry and Biology of the Isoquinoline Alkaloids*, Springer-Verlag, Berlin, 1985.
18 J.-P. Roduit, A. Wellig and A. Kiener, *Heterocycles*, 1997, **45**, 1687.
19 M. Ohno, M. Otsuka, M. Yagisawa, S. Kondo, H. Öppinger, H. Hoffmann, D. Sukatsch, L. Hepner and C. Male, *Antibiotics*, in *Ullmann's Encyclopedia of Industrial Chemistry*, ed. W. Gerhartz, VCH Verlagsgesellschaft, Weinheim, 1985.
20 J. Danzig, W. Tischer and C. Wandrey, *Chem. Eng. Technol.*, 1995, **18**, 256.
21 U. Giesecke, F. Wedekind and W. Tischer, *Dechema Biotechnol. Conf.*, 1992, Pt. B, 609.
22 A. Berry, S. Battist, G. Chotani, T. Dodge, S. Peck, S. Power and W. Weyler, *Proc. Biomass Conf. Am.: Energy, Environ., Agric. Ind.*, 1995, p. 1121.
23 J.-P. Kaiser, Y. Feng and J.-M. Bollag, *Microbiol. Rev.*, 1996, **60**, 483.
24 M. Nagel and J. R. Andreesen, *Arch. Microbiol.*, 1990, **154**, 605.
25 M. Yasuda, T. Sakamoto, R. Sashida, M. Ueda and Y. Morimoto, *Biosci. Biotechnol. Biochem.*, 1995, **59**, 572.
26 A. Kiener, *EP* 0,504,819 A2, 1992.
27 A. Kiener, R. Glöckler and K. Heinzmann, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1201.
28 T. Ishikawa, K. Maeda, K. Hayakawa and T. Kojima, *J. Mol. Catal. B*, 1996, **1**, 173.
29 M. Ueda and R. Sashida, *J. Mol. Catal. B*, 1998, **4**, 199.
30 M. Wieser, K. Heinzmann and A. Kiener, *Appl. Microbiol. Biotechnol.*, 1997, **48**, 174.
31 A. Kiener, Y. van Gameren and M. Bokel, *USP* 5,284,767, 1994.
32 S. Kagabu, K. Moriya, K. Shibuya, Y. Hattori, S. Tsuboi and K. Shiokawa, *Biosci. Biotechnol. Biochem.*, 1992, **56**, 362.
33 A. Kiener, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 774.
34 A. Kiener, *USP* 5,242,816, 1993.
35 H. Yamada and H. Kumagai, *Adv. Appl. Microbiol.*, 1975, **19**, 249.
36 M. Wieser, T. Yoshida and T. Nagasawa, *Tetrahedron Lett.*, 1998, **39**, 4309.
37 T. Nagasawa and H. Yamada, *Trends Biotechnol.*, 1989, **7**, 153.
38 U. Groeger, K. Drauz and H. Klenk, *Angew. Chem.*, 1992, **104**, 222.
39 M. Sauter, D. Venetz, F. Henzen, D. Schmidhalter, G. Pfaffen and O. Werbitzky, *PCT/WO* 97.33987, 1997.
40 C. Bernegger-Egli, K.-S. Etter, F. Studer, F. Brux and O. M. Birch, *J. Mol. Catal. B, Enzymatic*, 1999, **6**, 359.
41 H. Mori, T. Shibasaki, K. Yano and A. Ozaki, *J. Bacteriol.*, 1997, **179**, 5677.
42 R. Viani, *Coffee*, in *Ullmann's Encyclopedia of Industrial Chemistry*, ed. W. Gerhartz, VCH Verlagsgesellschaft, Weinheim, 1986.
43 Y. Asano, T. Komeda and H. Yamada, *Biosci. Biotechnol. Biochem.*, 1993, **57**, 1286.

*Paper 8/09538H*

# From fossil to green

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## Summary

In the year 2040 we will have to feed 9–10 billion people and to provide them with energy and materials. We want them to live according to the requirements of a developed society, and we do not want to pollute the earth or change the climate. The question addressed in this contribution is whether this scenario—sustainable technological growth—is technologically possible on a world wide basis. In 1996, more than 80% of the world's energy demands (350 EJ $a^{-1}$) originated from fossil resources (mineral oil, coal and gas) and the same holds for organic raw materials. In view of the exhaustion of fossil resources and environmental considerations, our radical hypothesis has been that we will no longer use fossil organic resources from, let's say, 2040 onwards.

Our natural resources are the sun, $CO_2$ in the atmosphere and land and water on the earth. It will be shown that these natural resources and the appropriate conversion technologies will enable us to move from the present fossil resources based economy to a plant-based economy as far as organic raw materialsare concerned. The sun will be the major source of energy.

The limiting factors in such a scenario are:

1 the amount of agricultural land available;

2 the ability of the world community to overcome the socio-economic and political problems in realising the scenario as formulated in the first paragraph of this abstract.

It will be illustrated which technologies need to be developed further and fine-tuned in the coming decades. Examples will be given how present-day bulk organic chemicals and materials can be approached from biomass. Methanol is expected to develop as a key chemical (and hydrogen-carrier). Moreover, one may consider a partial substitution of materials of today by "green" materials, that are directly or in a few reaction steps available from biomass, such as starch and polylactate, respectively.

One thing is certain: the plant will be the 'plant' of the future!

## Introduction

The era of a chemical industry based on fossil resources (*i.e.*, mineral oil, gas and coal) will gradually come to an end in the course of the next century. Two main reasons for this prediction are:

(1) The stocks of fossil resources are finite. First of all, mineral oil stocks will be exhausted around 2050 if we continue our present way of life. The times that more oil was found each year than was consumed are over. The present low oil prices should not confuse us. See the recent convincing article of Campbell and Laherrère.[1] Natural gas will last longer (some 75 years) and coal will last longest (> 200 years).

(2) Environmental considerations. All kinds of pollution from global warming to acid rain, from smog to ground water pollution, have been linked to the use of fossil fuels.

Hence we are really living on the threshold of a new era in chemistry—and unfortunately in most chemical research and education this fact is not sufficiently recognised. The background of this attitude lies undoubtedly in the fact that industry hardly invests in longer term research for economic reasons, whereas the universities for understandable reasons continue to do the type of research they are good at—*i.e.*, in a chemical context, petrochemistry. Of course, the above picture is black and white, and there are exceptions, but we advocate strongly the placement of much more emphasis on plant-based raw materials in research and in education.

In this contribution the radical starting hypothesis has been that from 2040 onwards we will no longer use fossil organic raw materials, as a consequence of exhaustion and environmental considerations. The fundamental question is raised: 'Is this technologically feasible while maintaining our present way of life in terms of food, organic materials and energy consumption?'.

## Situation analysis 1995 and prognoses for 2040

### Energy

In 1980, the world energy consumption amounted to about 350 EJ (E = exa = $10^{18}$) per annum with a world population of 5 billion, or, on average, 2200 W per capita. In the developed world this number varies from about 3400 W per capita in Japan to 10000 W per capita in the USA, whereas in the developing world this varies from 30 W per capita in Bangladesh to 620 W per capita in Brazil.

In Table 1 some critical global data are given. The fundamental questions arising from these data are whether it is at all possible, without fossil resources, to produce sufficient food (1st priority), organic materials (2nd priority) and energy (3rd priority) to allow 9–10 billion people[2] a decent life.

The present-day commercial energy demands are mainly (85%) met by fossil fuels (oil *ca.* 40%, coal *ca.* 25%, gas *ca.* 20%). Nuclear energy contributes about 5%, the same figure applies for hydroelectric power. The remaining 5% is divided over renewable sources such as biomass, solar energy, wind, *etc.* Some 14% of the energy consumption consists of non-commercial energy, mainly in the developing world, from biomass (straw, sugar cane, *etc.*).

## Green Context

**The development of sustainable routes to chemicals has often been overlooked since the discovery of plentiful oil supplies. However, with an increasing population, and oil stocks being finite, we now face a situation where we must use sustainable raw materials if the chemical industry is to survive. That is the claim made by the authors of this provocative analysis of the current state of the chemical industry. The paper develops a scenario which investigates the feasibility of actually achieving a sustainable plant-based chemical industry which could meet the needs of the planet's population in the middle of the next century, without impinging on agricultural land.** ***DJM***

**Table 1** Situation analysis 1995 and prognosis for 2040

| Critical global data: | 1995 | 2040 |
|---|---|---|
| Population | $5 \times 10^9$ | $10 \times 10^9$ |
| Energy consumption/EJ | 350 | 900 |
| Energy consumption per capita/W | 2200 | 3000 |
| Agricultural land/ha | $3.4 \times 10^9$ | $2.8 \times 10^9$ |
| Organic materials/ton | $0.3 \times 10^3$ | $1.0 \times 10^3$ |

ha = hectare = $10^4$ m$^2$.

The world reserves of economically exploitable fossil organic raw materials (oil, gas, coal) amounted to 35 700 EJ in 1991. Total reserves are speculated to be 260000 EJ. Hence, in 1991 there remained a stock of fossil fuel for about 100 years, based on the 1991 consumption (oil 50 years, gas 75 years, coal > 200 years). Of course, oil and gas exploration can prolong this period, but the fact remains that the stocks of fossil fuel are finite. Also, we would like to avoid an increase of $CO_2$ emission.

If we take into account that the expected growth of the world population is from 5 billion today to 9–10 billion in 2040 (*cf.* UN estimates) and that the world average energy consumption per capita will increase from 2200 W today to 3000 W in 2040 for a developed and more equalised society, then the energy needs in 2040 will be around 900 EJ or 2.5 times the present energy consumption.[3]

The sustained growth scenario requires switching from fossil fuel to renewable forms of energy and organic raw materials.

It is good to realise that until 1850 all organic consumer products and industrial raw materials were plant-based. Within the relatively short period of 150 years society changed from a mainly plant-based economy to an economy based on fossil fuels (coal until the end of the 19th century, until 1950 mineral oil, and now more and more natural gas). Wood supplied 70% of the fuel demand in 1870, in 1920 70% came from coal, in 1970 70% from mineral oil.

Let's return to renewable energy. For environmental and safety reasons we have abandoned nuclear energy in our scenario. Our nuclear reactor is the sun—at a safe distance from our planet. The sun applies advanced technology: nuclear fusion. The radiation of solar energy arriving on the earth is estimated to be $2.8 \times 10^6$ EJ a$^{-1}$, hence 3000 times the energy requirements in 2040. However, the amount that can be converted into useful energy is orders of magnitudes smaller. Renewable forms of energy are solar energy in various forms (different types of solar heating collectors ($T$ <100°C), solar mirrors ($T$ >100 °C) and photo-voltaic (PV) solar cells), energy based on wind-driven windmill parks, energy based on biomass, energy based on water power (hydroelectric, tidal, wave), geothermal energy, *etc.* In this contribution we will limit ourselves to solar energy and energy from biomass, because in the longer term they offer the best alternatives to fossil fuel. A key question is: 'Is it possible to harvest sufficient biomass, after deduction of the food needs of a world population of 10 billion, to produce the required amount of organic raw materials?' The answer to this question depends mainly on the yield of the photosynthesis and the amount of agricultural land available to produce biomass.

Although the learning curve will be long, PV cells and similar technologies based on the same principle are key factors[4,5] in the future large scale application of solar energy. The future of PV cells looks good, also economically: the EU expects[6] the same price for PV electricity as for fossil-based electricity by the year 2010. The same holds for the required amount of land to place the solar modules equipped with PV cells. To give an impression: the world wide electricity consumption in 1990 could be produced on 10 million ha—this figure can be compared, *e.g.*, with the 225 million ha required to produce the world wide wheat consumption.

In a scenario without fossil fuel, solar energy may also be the starting point of a hydrogen economy by electrolysis of water. Hydrogen gas is a clean and powerful fuel. Also, hydrogen is important in making $NH_3$, and reaction with CO (or $CO_2$) yields $CH_3OH$, a key chemical for the manufacture of other organic compounds.

This part on energy is concluded with a scenario as described by the Shell company[7,8] (Table 2). The Table speaks for itself.

**Table 2** Possible energy scenario 1990–2040[7,8]

| | 1990 | | 2040 | |
|---|---|---|---|---|
| Energy Source | EJ | ± % | EJ | ± % |
| Trad. biomass | 55 | 16 | 60 | 6 |
| Coal | 70 | 20 | 180 | 18 |
| Oil | 130 | 38 | 160 | 17 |
| Gas | 55 | 16 | 140 | 14 |
| Hydro | 18 | 5 | 50 | 5 |
| Nuclear | 17 | 5 | 60 | 6 |
| Wind | — | — | 70 | 7 |
| New biomass | — | — | 120 | 13 |
| Solar | — | — | 130 | 14 |
| Total | 350 | 100 | 1000 | 100 |

## Biomass

A plant is a 'growth machine': the above-ground part catches light and $CO_2$ (0.03% in the atmosphere), the below-ground part absorbs water and mineral nutrients. The combined intake enables the plant to produce—along ingenious routes—biomass that can be invested in growth above, and below, ground or stored. By photosynthesis, according to the reaction $n\mathrm{CO_2} + n\mathrm{H_2O} \longrightarrow (\mathrm{CH_2O})_n + n\mathrm{O_2}$, and by further biosynthesis numerous carbohydrates are formed, the composition of which depends on the type of plant. We are all familiar with monosaccharides (glucose and fructose), disaccharides (sucrose) and polysaccharides (*e.g.*, starch, cellulose, inulin). Moreover plants manufacture systems containing less oxygen, like triglycerides and terpenes, *etc.*

The maximum theoretical yield of photosynthesis, related to white light, is 6.6%. The maximum values reached in practice[9] are 2.4 to 3.2% for C4 plants (sugar cane, sorghum, corn, miscanthus) and 1.7 to 1.9% for C3 plants (sugar beet, eucalyptus). On average, the yield of photosynthesis is around 0.5%. Nevertheless, under favourable circumstances, 30–70 tons of dry biomass can be harvested per hectare and per annum. It is anticipated (see Rabbinge[10,11]) that plant breeding and genetic modification of plants will further increase the yields of biomass per hectare (and the biomass composition), though the growth will be less fast than before.[12] Thus global productivity increases (rises in cereal yields per hectare) have been reduced from 2.2% per year in the period 1967–1982 to 1.5% per year in 1982–1994.

According to Eggersdorfer *et al.*[13] the world biomass production amounts to 170 000 million tons per annum, of which, however, only 3% or 6000 million tons per annum are being cultivated, harvested and used (food and non-food). In Fig. 1, data about the quantities of renewable and fossil resources are given. Note that the total use figures (for 1992) for biomass and fossil resources are about the same.

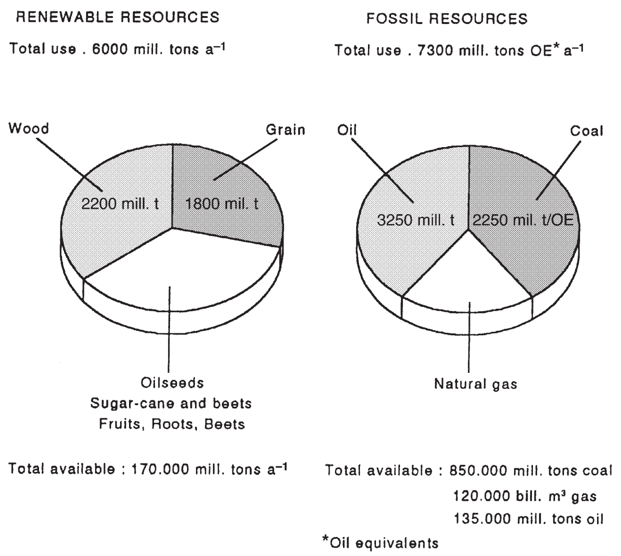

**Fig. 1** Renewable and fossil resources (after Eggersdorder *et al.*[13]).

More than 90% of fossil resources are used for energy generation and less than 10% for organic raw materials. Biomass production, apart from wood for paper (200 million tons per annum) and construction material, is mainly used for food.

The medium-term prospects for the production of organic materials and chemicals from biomass have been reviewed by Morris and Ahmed[14] under the provocative title '*The Carbohydrate Economy—Making Chemical and Industrial Materials from Plant Matter*'. The authors give many quantitative data as to how and for which products the transition from plant-based to fossil raw materials has taken place. They expect that in the next 50 years biomass will remain the main raw material for food production but will also become again a major raw material for the organo-chemical industry.

Before discussing how the desired materials can be made from biomass, we first need to answer the question of how much biomass can be produced on planet earth to:

a feed 9–10 billion people—first priority
b provide the population with the required organic materials—second priority
c make a contribution to the energy needs

In 1980, Bruin[8] reported extensive calculations on the energy flows in the agricultural/food system (see Fig. 2). Although the efficiency of photosynthesis is very low, the total result of photosynthesis is large. A flow of about 95 TW (1 TW = 31.7 EJ $a^{-1}$ is fixed in biomass, about 30 TW of which are in the form of poorly accessible phytoplankton in the oceans, about 45 TW are in forests and about 20 TW in other plants, 5 TW of the latter being contributed by agriculture. These flows are impressive indeed when compared to the present world energy consumption of about 9 TW. From Fig. 2 one may derive that the conversion yields from biomass to food and wood are low.

Food consumption amounts to 0.52 TW (= 2700 kcal per capita per day, in 1995). Wood for human use amounts to 1 TW, fossil fuels input is 9 TW. For the 1.52 TW of consumed biomass, 70 TW solar energy was used. When corrected for respiration losses, maintenance of terrestrial plants and forests, and for phytoplankton growth, a net energy consumption of about 37 TW yields 1.52 TW biomass (food and wood) for use by humans. Hence the yield of this conversion system is only 4%. In particular, the conversion of biomass to meat and milk *via* cattle has a very low yield.

## Scenario 2040

The assumptions for 2040 are summarised in Table 3. How much agricultural land will be required to feed 10 billion people with 2500 kcal $day^{-1}$? Bruin calculated[15] this for a standard daily diet per capita consisting of 480 g grain, 750 g milk and 80 g meat.

| | |
|---|---|
| Required for grain (22 tons $ha^{-1}$ $a^{-1}$) | : 159 × $10^6$ ha |
| Required for milk and meat | : 495 × $10^6$ ha |
| Oils and fats, vegetables, sugar, fruit, coffee, tea, *etc.* | : 833 × $10^6$ ha |

Assuming that the agricultural system functions with 75% of the maximum yield, we arrive at a figure of 2.0 × $10^9$ ha required for food production in 2040. In energy units, this agricultural system delivers: food 38 EJ $a^{-1}$ (= 4% of total energy requirement), straw 32 EJ $a^{-1}$, manure 16 EJ $a^{-1}$.

Hence, for non-food biomass production 0.8 × $10^9$ ha remain, which, at a maximum yield (estimate: 50 tons $ha^{-1}$ $a^{-1}$), may deliver 40 × $10^9$ tons $a^{-1}$ biomass. Without adverse ecological consequences, forests may deliver another 4 × $10^9$ tons $a^{-1}$. Waste streams are expected to contribute another 5 × $10^9$ tons $a^{-1}$. In conclusion, in 2040 there will be available for non-food application 50 × $10^9$ tons $a^{-1}$ of biomass, or about 25 ×$10^9$ tons of carbon for organics, which was our second priority after food.

We estimate the demand for organic raw materials to be 1000 × $10^6$ tons $a^{-1}$ in 2040 (presently 300 × $10^6$ tons $a^{-1}$), which, with a conversion yield of 20%, could be produced from 5 × $10^9$ ton biomass.

The third priority is energy from biomass. There still remains 45 × $10^9$ tons of biomass for this purpose, which could deliver in energy terms 45 × $10^9$ × 15 × $10^9$ × 0.3 or about 200 EJ $a^{-1}$.

This provides a substantial contribution to the energy needs of 2040 (935 EJ); the remainder has to come, in a scenario without fossil fuel, from solar energy and other forms of renewable resources (water, wind, geothermal, *etc.*). It may be noted that our figure of 200 EJ energy contribution from biomass in 2040 corresponds reasonably well with the figures (Table 2) provided by Shell (180 EJ in 2040).

From all that has been said so far it will be clear that our conclusions are very sensitive to:

* maximum available agricultural land
* water supply
* yield of agricultural system
* size of world population
* energy consumption per capita
* conversion yields of biomass to organic materials and energy

## Conditions

There are a number of conditions underlying the biomass availability conclusion.

1. The conclusion is valid judged from a global perspective. At regional and national levels enormous differences may occur depending on the degree of technical development, climate, nature of the soil and socio-economic factors.
2. The scenario proposed requires a world-wide infrastructure, *e.g.*, certain agricultural products especially where the yield is highest, PV cells particularly where most solar energy can be harvested, *etc.* This global infrastructure will be difficult to realise from a political and social point of view.
3. The conclusion holds only under the condition of continuing technological progress with a time horizon of more than 10 years. This is a heavy responsibility for national governments, the European Union and the United Nations.

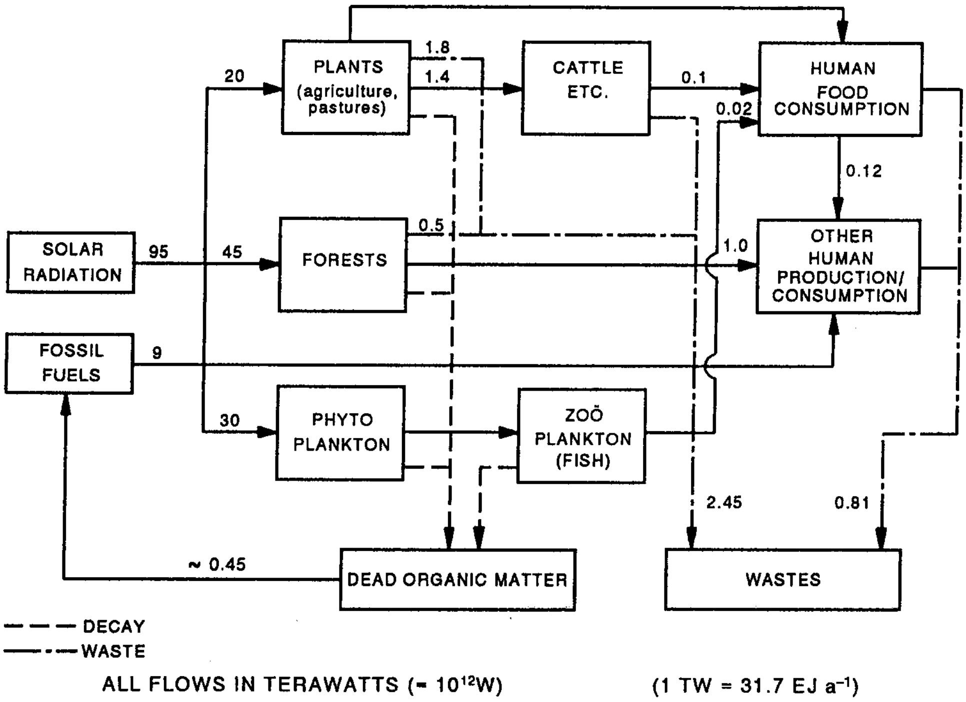

**Fig. 2** Energy flows in the agricultural/food system.[8]

**Table 3** Assumptions scenario 2040

| | |
|---|---|
| World population | $10 \times 10^9$ |
| Available agricultural land/ha | $2.8 \times 10^9$ |
| Tropical forest/ha | $3.7 \times 10^9$ |
| Forest in moderate climate/ha | $1.7 \times 10^9$ |
| Urban area/ha | $1.0 \times 10^9$ |
| Deserts, tundra *etc.*/ha | $2.0 \times 10^9$ |
| Food per capita/W; kcal day$^{-1}$ | 120; 2500 |
| Food total per annum/TW; EJ a$^{-1}$ | 1.2; 38 |
| Energy per capita/W | 3000 |
| Energy total/TW; EJ a$^{-1}$ | 30; 935 |
| Organic materials/tonnes a$^{-1}$ | $1000 \times 10^6$ |

4. There is no reason for pessimism regarding the required yield improvement in agriculture. Rabbinge[10,11] pointed to the fact that, despite the growth in population, the food situation in the world has improved considerably during the last 100 years, even to the extent that Europe and the USA have difficulties in coping with the food surpluses as a consequence of the continuing productivity improvement in agriculture, *e.g.*, from 2 tonnes wheat per hectare in 1900 to 8 tonnes wheat per hectare in Europe today. The authors also calculated that, if the agricultural land in Europe were optimally used, the total European harvest of agricultural products could be produced on 50 million ha as compared with 130 million ha today.
5. Our conclusion is based on optimum agricultural yields. These can only be reached by growing plants in areas where the conditions for those plants are optimal (availability of water, nutrients, *etc.*). In optimising the world agricultural system, plant breeding, plant biotechnology, and expert computer systems will play an important role. Expert computer systems will enable the agrarian to control plant diseases, to reduce water consumption and to manage the various crops efficiently.
6. Genetically-modified crops should be accepted world-wide. In view of the rapid developments in North America, the authors feel confident about this.
7. Overall, we cannot escape the conclusion that, in 2040, sustainable technology will also be able to deliver the required products, but that the real core of the sustainability problem is of socio-political nature (where to produce what).

## Biomass as raw material for organic materials and chemicals

Biomass may be utilised in different ways to provide us with organic compounds and materials:

a. Nature already produces the desired structures and isolation of these components mostly requires only physical methods.

   *Examples:* polysaccharides (cellulose, starch, alginate, pectin, agar, chitin, inulin, *etc.*), disaccharides (sucrose and lactose), triglycerides, lecithin, natural rubber, gelatin, flavours and fragrances, *etc.*

   Some present-day production volumes are sucrose $115 \times 10^6$ t a$^{-1}$, triglycerides $85 \times 10^6$ t a$^{-1}$, natural rubber $5.5 \times 10^6$ t a$^{-1}$. Cotton, the natural cellulose fiber,[16] is produced in a volume of $20 \times 10^6$ t a$^{-1}$, an amount which equals the sum[17] of all synthetic fibers (volume order: polyester > polyamide > acrylic).

   The possibilities to produce organic chemicals directly by and from the plant by means of plant biotechnology will increase dramatically. The plant is the ‘plant’ of the future.

b. One step (bio)chemical modification of naturally produced structures under a.

   *Examples:* cellulose and starch derivatives, glucose and fructose, glycerol, fatty acids; ethanol, citric acid, glutamic acid and lactic acid by fermentation. Lactulose, lactitol and lactobionic acid by isomerization, hydrogenation and oxidation, respectively, from lactose. Nature offers various fine starting materials for pharmaceuticals. Thus morphine is converted by one methylation step into the cough medicine codeine (200 t a$^{-1}$) (whereas one acetylation step leads to heroin).

c. In several steps organic chemicals and organic materials are obtained from natural products.

*Examples* include: ethanol can be converted to today's No. 1 organic chemical, ethylene; sorbitol and mannitol by hydrogenation of glucose and sucrose, respectively; vitamin C in several steps from glucose; (*S*)-β-hydroxy-t-butyrolactone in two steps from lactose;[18] (−)-menthol in six steps from β-pinene;[19] fatty alcohols and amines from triglycerides; alkyl polyglucosides from glucose and fatty alcohols, *etc.*; succinic acid from glucose and $CO_2$ (!).[20]

d. 'Back to $C_1$-Chemistry' by using biomass as the carbon and hydrogen source, converting it into small fragments (synthesis gas) and building it up again to the desired structures.

In the above the focus has been on chemical structures and less on the product areas. For some large product groups it can be stated that the green label (renewables-based) is accepted as a selling advantage. We mention: flavours and fragrances; cosmetics; adhesives; lubricants; detergent formulations; agrochemicals.

## Primary conversion technologies of biomass

In Fig. 3, an overview is given of the candidate primary conversion technologies of biomass, ranked according to water content. The three most important technologies will be dealt with in some detail.

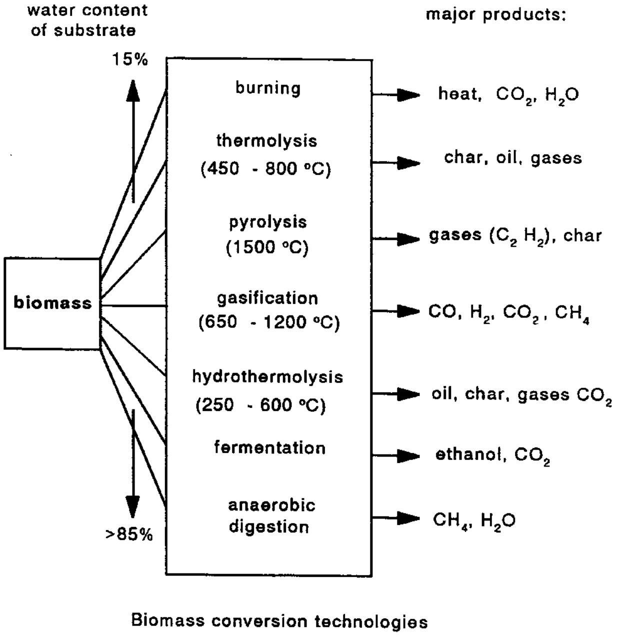

**Fig. 3** Biomass conversion technologies.

### *Gasification*

Biomass can be converted into power plant fuel by gasification[21] with a high yield and in an environmentally friendly fashion. Also, in the longer term, the economics of this process look good, notably for energy crops. The gasification takes place with air, at temperatures of around 850 °C. The gas consists of 13% $H_2$, 17% CO, 4% $CH_4$, 12% $CO_2$, 13% $H_2O$ and 40% $N_2$ with a caloric value of 6 MJ $m^{-3}$.

In the 2040 scenario, 80 EJ $a^{-1}$ could be produced from waste streams and 200 EJ $a^{-1}$ from energy crops, on a global scale. The removal of sulfur-containing components, tar, char and ash from the gas is critical for use in gas turbines and for methanol production. The technology is promising. Many pilot plants are in operation, large installations are in the planning phase. The gas could presumably also be used in Fischer–Tropsch synthesis.

### *Hydrothermolysis*

During the period 1982–1993, the Royal Dutch Shell Laboratory developed a process to convert biomass into liquid fuel, so-called bio-crude.[22] This process is called HTU (Hydro-Thermal Upgrading). First biomass is treated in an aqueous slurry at 200 °C and 30 bar, followed by a treatment at 330 °C and 200 bar. This process results in a bio-crude, an oil with low oxygen content, which can be further upgraded by a catalytic hydrodeoxygenation step to a high quality naphtha or diesel oil with very low oxygen, nitrogen and sulfur contents. The oil yield is about 40% based on the biomass feed stock. Wood, agricultural and domestic (green) waste streams were successfully applied as feed stocks. According to Shell, this HTU process is the cheapest route to liquid biofuels. Its cost price would be in the order of \$20–40 per barrel,[22] as compared with fossil crude oil today at about \$12 per barrel. Hence, the process is not yet economical under the present tax regime. This HTU process and many variants of this process lead directly to bio-crude, from which the known transport fuels and petrochemicals can be manufactured, without the extra sulfur-removing steps, *etc.*, which are necessary with fossil fuel.

### *Fermentation to ethanol*

By fermentation of biomass (sugars, grain, cellulose, *etc.*) with yeast a 6.5–11% ethanol in water solution is formed,[23] from which 95 or 100% ethanol can be obtained by distillation (or membrane-filtration, or distillation-adsorption). Depending on the feed stock, a chemical or enzymatic hydrolysis is sometimes required first, to convert the biomass into monosaccharides. Alcohol is a raw material for many organic chemicals among which, as was already mentioned, today's No. 1 organic chemical, ethylene. In India over 400 000 t $a^{-1}$ of alcohol is used[24] in making 'alco-chemicals' with acetic acid and ethylene glycol as the numbers 1 and 2. Moreover, in India and China aqueous alcohol is directly applied in aromatic ethylation (ethylbenzene, 1,4-diethylbenzene and 4-ethyltoluene). Ethanol can also be used directly as a liquid fuel. The technology is well developed and applied on a large scale in the USA (corn-based) and in Brazil (sugar cane-based). It is expected that, as a result of better enzymatic hydrolysis and ethanol processing together with rising fossil fuel prices, bioethanol prices will become competitive with gasoline in 2010.

## A hydrogen economy?

Solar energy, by means of PV or similar cells, will be (in the authors' opinion) a main source of energy in the future. This technology seems essential in creating sustainable technological growth without fossil resources.

Assuming that:

a. 1% of the sunlight received by our planet ($2.8 \times 10^6$ EJ $a^{-1}$) is captured by solar cells;

b. the efficiency of the conversion from solar energy to electricity amounts to 20%;

c. the yield of electrolysis of water by solar electricity is 60%; an energy-equivalent of 3360 EJ $a^{-1}$ could be produced in the form of hydrogen, which amounts to more than three times the required energy in 2040!

Many improvements of the technology are possible; the choice of the semi-conductor material, generally silicon, the fixation of this material on film, the lay-out of modules, the architecture of modules, the storage of energy in batteries and in accumulators, *etc.*

A step to 'artificial' photosynthesis is the development of the Grätzel cell[5] by adsorption of a ruthenium complex on nanocrystalline $TiO_2$. Owing to the large surface area of the $TiO_2$, the yield of these solar cells is higher than that of conventional PV cells. As stated before, solar energy can lead directly to $H_2$ as a key chemical for many applications. $H_2$ may be used as such (*e.g.*, fuel in space shuttles) or stored in metals such as Pd. Hydrogen can also be stored chemically by reaction with, *e.g.*, $CO_2$ to $CH_3OH$. In turn, $CH_3OH$ is a very good liquid fuel and a key chemical in the production of many organic chemicals.[25] Fig. 4 shows the versatility of methanol as a starting compound.

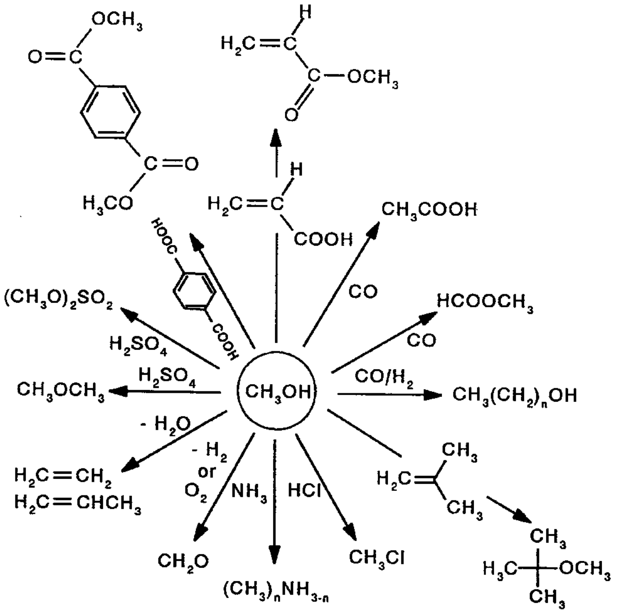

**Fig. 4** Methanol as a key chemical.

In the decades to come hydrogen may also play an important role as hydrocarbon-derived fuel in fuel-cell engined cars. In the Shell/Daimler/Ford/Ballard concept conventional transport fuels are converted in a number of catalytic steps to $H_2$ and $CO_2$ after which hydrogen acts as clean fuel. The art is to get the CO content down to a few ppm.

In conclusion, $H_2$ is a powerful energy carrier and, *via* methanol, an essential starting material for (bulk) chemicals. Therefore, we may witness the start of a hydrogen-based economy, together with the plant-based economy.

## Approach of the present top organic materials

We have investigated how the current top eight organic materials could be made from biomass. These top eight (in volume, 1998) are: polyethylene (48 × $10^6$ t), polypropylene (23 × $10^6$ t), polyvinyl chloride (26 × $10^6$ t), polyethylene terephthalate (13 × $10^6$ t), polystyrene (14 × $10^6$ t), butadiene/co-polymers (8 × $10^6$ t), phenol resins (5.5 × $10^6$ t) and polyamides (4 × $10^6$ t).[26]

The following remarks—by way of examples—can be made:

### *Polyethylene*

An obvious route (*cf.* Fig. 5) is from carbohydrates to ethanol and to ethylene. Substantial mass decrease occurs. Another route to the monomers ethylene and propylene is the selective conversion of methanol over suitable zeolites to a package of $C_2$, $C_3$ and $C_4$ olefins. It may be noted that the monomer ethylene (*ca.* 75 × $10^6$ t $a^{-1}$) is also the starting compound for the bulk chemicals ethylene oxide, ethylene glycol, ethylbenzene and styrene.

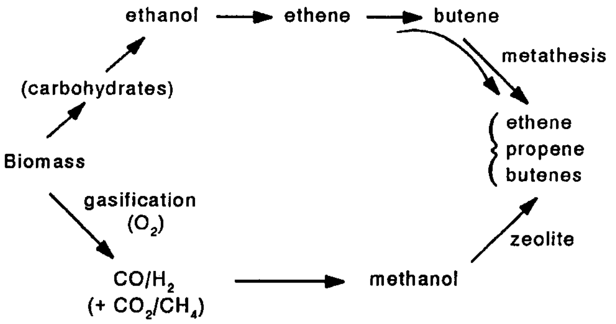

**Fig. 5** Biomass-based routes to lower olefins.

### *Polypropylene*

Here the methanol-to-olefins (MTO) process[27] seems the appropriate route of the future. The monomer (≈45 × $10^6$ t $a^{-1}$) also serves the bulk compounds propylene oxide, acrylonitrile, acrolein and acrylic acid as a starting chemical.

### *Butadiene (co-)polymers*

Ethanol can be converted into butadiene by the reaction sequence dehydrogenation to acetaldehyde, aldol condensation, dehydration. This sequence can be carried out in one process step[28] over a MgO–$SiO_2$ catalyst (Lebedew process) which seems an interesting option.

### *Polystyrene*

Diels–Alder cyclo-addition of butadiene over a Cu(I) zeolite gives vinylcyclohexene in excellent yield (Fig. 6).[29] Recently the technology has been developed to convert vinylcyclohexene directly into styrene.

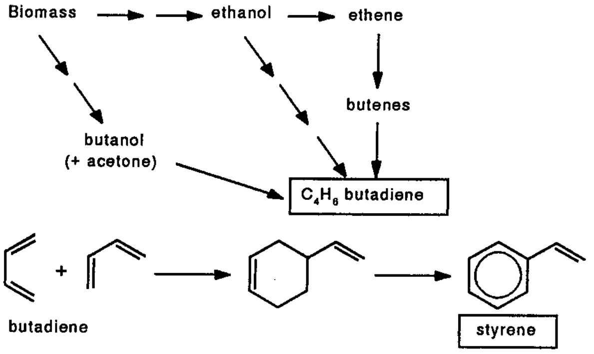

**Fig. 6** Biomass-based routes to butadiene and styrene.

### *Polyalkylene terephthalates*

Here the most important and still fast growing material is based on ethylene glycol and dimethyl terephthalate. Fig. 7 shows two green routes to terephthalic acid. The two-step route based on the cheap terpene limonene, seems the method of choice. The sequence starting from fructose consists of more steps than the limonene route and involves one difficult step: the Diels–Alder addition of ethylene to 2,5-furandicarboxylic acid. It may be noted that nature rarely delivers aromatic structures. Exceptions are the complex wood constituent lignin and the natural crosslinking agent ferulic acid. The question arises whether 2,5-furandicarboxylic acid could develop towards a ‘bioterephthalic acid’ by acting as a monomer in preparing polyesters and polyamides.

As to the diol component of the polyalkylene terephthalates, green routes are as follows:

(i) ethylene glycol *via* ethanol, ethene, ethene oxide,

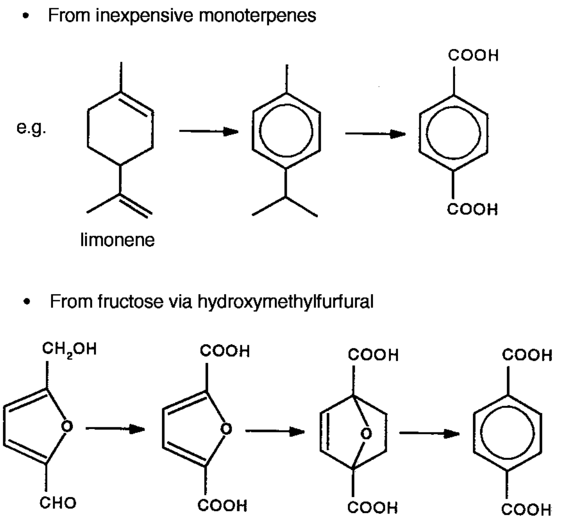

**Fig. 7** Green routes to terephthalic acid.

(ii) 1,4-butanediol by hydrogenation of succinic acid (ex glucose/carbon dioxide), and

(iii) 1,3-propanediol by fermentation of glucose as recently announced by DuPont.

The latter process will enter into competition with the conventional 1,3-propanediol process *via* acrolein (Degussa) and the modern ethene oxide/carbon monoxide process (Shell).

## Substituting petro-based materials by green materials

Although novel synthetic routes need to be developed when starting from biomass rather than from fossil organic material to produce the 'top eight' bulk materials, it seems to be technologically feasible. On the other hand, when the raw material source shifts from fossil to green, new materials will be discovered and developed with the same or new properties. See for instance the possibilities (Fig. 8) offered by the abundant natural mono-unsaturated $C_{18}$-acid oleic acid.[30] Upon oxidation or metathesis $C_9$- and $C_{18}$-dicarboxylic acids, respectively, are obtained that may constitute valuable monomers for new polymeric materials.

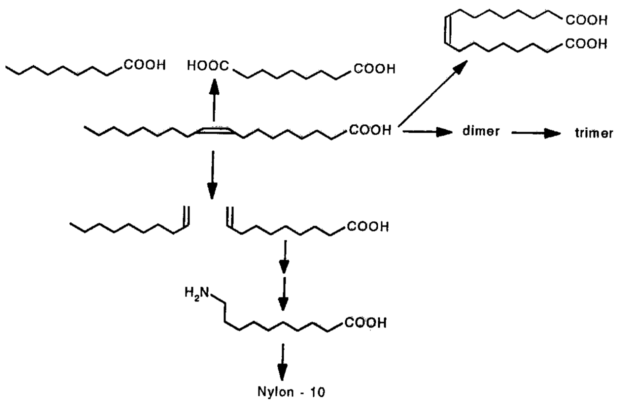

**Fig. 8** Oleic acid as key chemical.

Moreover, we mention in this context:

— processed starch (*e.g.* with some glycerol or sorbitol added) as a biodegradable substitute of non-biodegradable polystyrene foam, *e.g.* in packaging applications;

— poly-L-lactate (PURAC, NL) as a high-value biodegradable material for surgery and at short notice technical poly-L-lactate (Dow Chemical/Cargill) will be manufactured for relatively low-cost applications in which biodegradability is an issue;

— nonionic surfactants obtained by alkylation (or acylation) of mono- and disaccharides (Fig. 9).

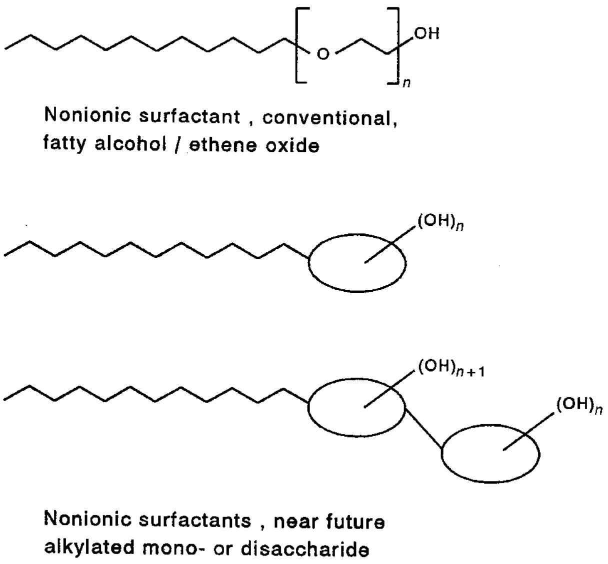

**Fig. 9** Alkylated sugars, nonionic surfactants.

Here two natural sources join forces: the triglycerides, which provide (by transesterification and hydrogenation) the fatty alcohols, and the sugars which replace the petrochemical ethylene oxide as the hydrophilic part of the surfactant. Note that the sugar is able to supply much more structural variation than ethylene oxide.

Alkylated glucose (APG, 70 000 t a$^{-1}$, Henkel AG) is already on the market.[31] In our group the alkylation of fructose has been studied.[32] Other commercial products include sorbitan esters, *N*-methyl gluconamides and sucrose fatty acid esters.

## Life cycle inventory and analysis

Of course a fair comparison between petrochemical- and renewable-based products requires an analysis of all inputs and emissions involved.

A life cycle inventory (LCI) covers the growing or mining of the raw materials, all energy components involved during transport and processing, emissions to air and water, *etc.*, up to the end-product. An LCI is part of the complete life cycle analysis (LCA). LCIs have become popularly known as "cradle to factory gate studies" whereas LCAs are named 'cradle to grave studies'.

LCIs for conventional as well as for fully renewable-based surfactants have been made by Henkel workers.[33] In a recent UK project[34] LCAs were made for several surfactants and lubricants and point to environmental advantages of oleochemical over petrochemical feedstocks.

## Some conclusions

* Scenario 2040 (almost doubling of world population, higher average standard of living, reduction of environmental pollution) seems technologically possible without the utilisation of fossil resources.

* This technological approach requires, amongst other things, the massive development and application of solar energy and biomass for food, organic raw materials, and energy.

- The plant will be the 'plant' of the future.
- Ultimately the limit to global growth will be the amount of agricultural land on earth.
- Biomass conversion to organic raw materials is able to replace the existing organic chemistry which is mainly based on fossil resources while adding structurally new materials.
- Altogether, much creativity is required of mankind.

## References

1 C. J. Campbell and J. H. Laherrère, *The End of Cheap Oil*, in *Sci. Am.*, March 1998, p. 60.

2 UN estimates, medium fertility, see *National Geographic*, October 1998, Millennium supplement: population. *NB* If the average woman's fertility is 2.6 then the population will be 27 billion in 2150; if it is 1.6 the total will drop to 3.6 billion in the year 2150. If fertility stabilizes at 2.0 the number will be 10.8 billion.

3 C. Okkerse and H. van Bekkum, in *Starch 96*, ed. H. van Doren and N. van Swaay, Zestec bv/Carbohydrate Research Foundation, The Hague, 1997, p. 1.

4 D. T. N. Kimman, *Chemisch Magazine*, October 1995, 431.

5 A. Hagfeldt and M. Gratzel, *Chem. Rev.*, 1995, **95**, 49.

6 The European Renewable Energy Study (TERES). ISBN 92-826-6450-3 (volumes 1 to 4) Brussels–Luxembourg, 1994.

7 Shell Briefing Service, November 1994, Renewable Energy.

8 Shell Selected Paper, Peter Kassler, November 1994.

9 J. A. Barsham, *Soil and Crop Science Society of Florida, Proceedings*, 1983, **42**, 2.

10 R. Rabbinge, *Simulation Monographs*, Pudoc, Wageningen, 1990, vol. 34.

11 R. Rabbinge, *Chemisch Magazine*, October 1995, p. 427.

12 C. C. Mann, *Crop Scientists seek a New Revolution*, in *Science*, 1999, **283**, 310.

13 M. Eggersdorfer, J. Meijer and P. Eckes, *FEMS Microbiol. Rev.*, 1992, **103**, 355.

14 D. Morris and I. Ahmed, *The Carbohydrate Economy*, Institute for Local Self-Reliance, Washington DC, August 1992.

15 S. Bruin, *Lecture: Biomass as a source of energy*, presented at 13th International TNO Conference, Rotterdam, 27 and 28 March, 1980.

16 H.-G. Fritz *et al.*, *Study on production of thermoplastics and fibres based mainly on biological materials*, Directorate-General XII, European Commission, 1994.

17 AKZO-Nobel brochure: *Man-made fibers*, in 1994.

18 *Chem. Eng. News*, July 13, 1998, p. 66.

19 R. A. Sheldon, *Chirotechnology*, Marcel Dekker, Inc., New York, 1993, p. 304.

20 M. J. van der Werf, M. V. Guettlez, M. K. Jain and J. G. Zeikus, *Arch Microbiol.*, 1997, **167**, 332.

21 C. D. Ouwens, *Chemisch Magazine*, October 1995, p. 442.

22 F. Goudriaan, *Chemisch Weekblad*, 1995, **34**, 3 and personal communication.

23 B. Mouris, *Chem. Ind.*, 18 June 1984, p. 435.

24 A. M. Kadakia, *Chemical Weekly*, August 5, 1997, p. 137.

25 J. R. Crocco, *Hydrocarbon Processing*, May 1994, 66 C.

26 W. C. Kuhlke, *Hydrocarbon Processing*, May 1994, p. 57.

27 I. E. Maxwell and W. H. J. Stork, *Stud. Surf. Sci. Catal.*, 1991, **58**, 616.

28 K. Weissermel and H.-J. Arpe, *Industrial Organic Chemistry*, 2nd edn., VCH, Weinheim, 1993.

29 I. E. Maxwell, R. S. Downing, J. J. de Boer and S. A. van Langen, *J. Catal.*, 1980, **61**, 485; 493.

30 S. Warwel, P. Bavaj, M. Rüsch and B. Wolff, in *Perspektiven Nachwachsender Rohstoffe in der Chemie*, ed. H. Eierdanz, VCH, Weinheim, 1996, p. 119.

31 *APG News* 1/95, Publication of Henkel Oleochemie.

32 A. M. van der Heijden, Thesis, Delft University of Technology, 1999.

33 F. Hirsinger *et al.*, *Tenside Surf. Det.*, 1995, **32**, 128; 171; 193; 398; 420.

34 P. S. Wightman, R. M. Eavis, S. E. Batchelor, K. C. Walker and S. P. Carruthers, *Cost Benefit Assessment including Life Cycle Assessment, of oils produced from UK-grown crops compared with mineral oils. Cf. Green Chemistry*, February 1999, G6/G7.

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