chemistry

that the resources are limited, green chemistry looks somewhat different through Canadian eyes. The two areas I would like to consider are the uses of green chemistry in resource industries and enhancements to green chemistry that can be achieved through the use of analytical chemistry. Here I freely admit to a bias. I am an analytical chemist. Throughout my career I have been involved with a number of environmental issues, including the Niagara River and its pollution by industries (remember Love Canal?) and a number of local pollution issues. So it is important to me that analytical chemistry be used to measure more than our failure to be stewards of the environment, but also to provide the means of

chimney. It solved the problem for Sudbury, but it made the residents of the Ottawa River Valley upset, as the acidification reached further east and was spread over a larger area. A partial solution was achieved when INCO eliminated the pyrrhotite by flotation, increased the oxygen level of the oxidizing gas and collected the SO_2 by-product, which it sold as sulfuric acid. The pyrrhotite, which, if left exposed, would be oxidized by bacteria to H_2SO_4 (the infamous 'acid mine drainage'), was reburied under anoxic conditions so that the extent of acid mine drainage would be reduced. As a reduction in the release of harmful by-products, this green chemistry reduced Canada's acid emissions by a significant percent. Consider the case of gold. Gold continues to be extracted using high concentrations of cyanide to form $Au(CN)_2^-$. Storage of waste cyanide in ponds results in ground water infiltration, leakage from poorly constructed dams, *etc*. A number of other compounds form stable complexes with gold and could be used in place of cyanide, such as thiourea or thiocyanate.

As the natural resources are used up in the world, chemists and biotechnologists are being asked to come up with innovative ways in which renewable resources can be used to replace non-renewable ones But there will continue to be a demand for some non-renewable resources. In my high school chemistry text, I remember clearly the figure that showed the extraction of copper from the deposits in Northern Ontario. Basically you filled a hole with copper sulfate solution, popped in a copper electrode in the solution and banged in a connector to the massive deposits of native copper and electrolyzed away until the copper boulder dissolved. What is the percentage copper in high-grade ore today? So

1 P. T. Anastas and T. C. Williamson, Green Chemistry, American Chemical Society, Washington, D.C., 1996.
2 Our Common Future, World Commission on Environment and Development (the Bruntland Commission), Oxford University Press, Oxford, 1987.

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There is increasing demand for hemp as a source of fibre

Potential for hemp as green fibre source

According to *Farmers Weekly* (17 September 1999) hemp is set to become and important green crop for arable rotation because of growing demand for hemp fibre from existing and new markets. Cigarette paper production has traditionally consumed a lot of hemp fibre, but it is now also being used as an alternative to cotton waste and wood pulp to make a range of environmentally acceptable papers. The second new market with huge potential is for lightweight door panels for the automotive industry. Automotive manufacturers in Germany are particularly interested in using a hemp and flax fibre mixture to replace the short wood fibres and to provide added strength and a significant weight reduction.

Gas-to-liquid technology

Rentech Inc has signed a letter of intent with Oroboros AB, headquartered in Goteborg, Sweden, to negotiate a licence for a GTL plant that will convert industrial off gases from a Swedish steel works into clean alternative fuels. The steel facility currently generates around 27 M cu ft/day of off-gases that are now flared into the atmosphere. The flaring, which occurs daily, produces about 2000 tonnes/year of carbon dioxide, a greenhouse gas. By implementing Rentech's GTL technology, the plant's off-gases, a mixture of hydrogen and carbon monoxide, can be converted into clean usable products instead of being flared. The application of Rentech's process to this one facility is estimated to reduce carbon dioxide emissions in Sweden by 200,000 tonnes/year. Oroboros plans to produce what it refers to as an Eco-Paraffin, a clean alternative fuel, from the GTL process. This fuel, also known as Fischer–Tropsch diesel, contains no sulfur or aromatic compounds. Moreover, based on an assessment by Oroboros, Eco-Paraffin may also have a lower production cost than other alternative fuels presently available in Sweden. Rentech Inc, the Denver-based holding company which developed and licenses a proprietary and patented process, gas-to-liquid (GTL), for the conversion of gases, solid and liquid carbon bearing material into valuable liquid hydrocarbons.

For further information see http://www.gastoliquids.com

Biomass

biodegradable solvent from…

USANTEC Inc. and Archer Daniels Midland have signed an agreement to jointly develop and commercialize new markets for ethyl lactate, a biodegradable solvent made from corn. Under the auspices of this arrangement, all North American sales of ethyl lactate manufactured by Archer Daniels Midland will be handled under the umbrella of a strategic relationship between NTEC and Archer Daniels Midland. This product, already being shipped to several customers in the US, is sold under the 'Versol' brand name. Ethyl lactate is a high performance, environmentally friendly green solvent that can successfully replace hundreds of millions of pounds of toxic petroleum-based chemical compounds used in the world today. Ethyl lactate is 100% biodegradable: it simply decomposes into carbon dioxide and water. Archer Daniels Midland, based in Decatur, Illinois, is engaged in the business of procuring, transporting, storing, processing and merchandising agricultural commodities and products.

For further information see http://www.admworld.com

liquid fuel from…

The HTU (Hydro Thermal Upgrading) process developed by Shell Nederland, Stork, Biofuel, TNO-MEP, Biomass Technology Group, and other bodies allows the production of green crude oil from biomass. The oil is intended for use as a traditional mineral oil fuel. The technology contributes to the government's target of increasing the amount of energy generated from biomass. It involves the conversion of water and residual plant materials to a liquid crude oil at high temperature and pressure. The oil is more environmentally friendly than mineral oil because its formation and breakdown are overall carbon dioxide-neutral.

polyesters from…

Metabolix Inc. of Cambridge, Massachusetts, USA, has been awarded a European Patent describing the production of polyesters in plant crops. The polyesters, known as PHAs, can be used as thermoplastics in an extensive range of applications. In parallel, Metabolix has also developed energy efficient fermentation routes to convert plant derived feedstocks into aqueous based PHA coating compositions. The PHA polyester materials may also be readily broken down to useful chemicals providing an alternative environmentally attractive and economical route for the sustainable production of chemical intermediates. The European Patent No. 482 077 brings the number of patents issued or exclusively licensed to Metabolix for the production of plastics and chemicals from agricultural sources to a total of eleven.

For further information see http://www.metabolix.com

Genetic modification

…in rubber production

The International Rubber Research and Development Board (IRRDB) are advocating a policy of using genetic research and development to ensure future sustainable supplies of natural rubber. The Board also maintains that the technological excellence of natural rubber cannot currently be matched by synthetic rubber. The production of natural rubber is also seen to serve the interests of the global environment by reducing deforestation and carbon dioxide levels throughout the world. The fact that natural rubber production is being forced into areas with poorer climate and soil properties is cited as further reason for the use of genetic development of clones.

…in agriculture

Monsanto Chairman and Chief Executive Officer Robert Shapiro has urged Greenpeace leaders and other stakeholders to engage with the company in an open and constructive dialogue about the use of biotechnology in agriculture. Shapiro reaffirmed that Monsanto continues to be a strong proponent of modern biotechnology as a safe and important tool for helping farmers meet the world's growing need for food and fibre in a more environmentally sustainable way. The exchange with Greenpeace leaders followed an announcement on 4 October 1999 by Monsanto that the company would not commercialize sterile seed technologies. Monsanto made the commitment in response to concerns of experts and stakeholders, including growers in developed countries, about the potential effect of gene protection systems in developing countries.

For further information see http://www.monsanto.com

Coatings systems for braided fuel hose

Kaechele-Cama Latex GmbH, of Eichenzell, Germany, has developed an environment-friendly solvent-free adhesive and coating system for braided fuel hose used in automotive and other applications. The patented system, applied to the hose by immersion, is based on Neoprene polychloroprene elastomer by DuPont Dow Elastomers. Fuel hose for modern motors, whether diesel or petrol, is exposed to high temperatures, corrosive fluids and other aggressive conditions. To meet such tough requirements automotive engineers normally specify braided, coated rubber hose. Until now solvent-based primers were mainly used to bind the textile layers to the rubber in this type of hose. The adhesive force of these primers results from their etching effect on the rubber. Solvents which evaporate during the manufacturing process are known to have undesirable effects on the environment and on employees producing the hose manufacturers have therefore been developing solvent-free systems. KCL's water-based adhesive and coating systems meet the automotive industry's demanding requirements as well as current and foreseeable environmental protection regulations. The product's cross-linking characteristics allow co-vulcanisation with the rubber of the hose itself. The KCL is not subject to gelling or clotting, even after extended stand times. Apart from the immersion process which is the usual one for hose production, the KCL system can also be applied by means of spraying or dipping.

The silane business

More than DM 500 M is to be invested by Degussa-Huels AG in its silane operations. By the beginning of 2002, capacity for production of sulfur-functional organosilanes is to be raised by two-thirds at a cost of DM 200 M. The major application for these compounds is in the rubber industry for production of green tyres. Capacity for chlorosilanes and organosilanes will be increased at a cost of DM 300 M, with the majority of the work due to be completed by 2002. The leading global producer of sulfur-functional organosilanes, Degussa-Huels is the second largest producer of organosilanes and chlorosilanes. It is the leading European producer. Demand for the compounds in recent years has been greater than the rate of economic growth and this is expected to continue. In early 2000, capacity expansions for sulfur-functional organosilanes are due to be brought onstream in Antwerp and Mobile, USA. A new production facility is due to be constructed in Antwerp. Further production capacity for organosilanes and chlorosilanes is to be added at the company's facilities in Antwerp, Mobile and Rhinefelden.

Phthalates in children's toys

We reported in a previous edition of *Green Chemistry* the background to the controversy over phthalates in children's toys and the various calls for a ban on their use (*Green Chem.* 1999, **1**, 102); we also reported the development of the Dutch Migration Test to measure phthalate migration. Now the European Commission has proposed an EU-wide ban on soft PVC teething toys for children under 3 years of age, after its Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) concluded that the Dutch Migration Test showed 'poor reproducibility'. Under the proposals other toys containing phthalates, but not intended for teething, would merely have to carry a warning to keep them out of the mouth. These proposals will now move to the Product Safety Emergencies Committee of the Member States.

Following talks with the British Toy and Hobby Association, the UK Department of Trade and Industry has announced an immediate ban on teethers and teething rings containing phthalates. Greenpeace has welcomed the ban but feels that it should not be restricted to teething toys, while the European Council for Plasticisers and Intermediates (ECPI), which represents manufacturers of phthalates, has reacted angrily to the ban, calling it 'totally unjustified'.

Cleaner fuels

…BP Amoco in Chicago

BP Amoco intends to bring three grades of cleaner gasoline to Chicago, and that the resulting emissions reduction would be the equivalent of removing 70,500 cars from Chicago's highways each day. The company reported that the announcement is a direct result of its ongoing partnership with General Motors Corp, through which the companies plan to offer consumers new choices for cleaner vehicles in the 21st century. BP Amoco announced that its first lower sulfur product offering in Chicago, its Crystal Clear Amoco Ultimate is available at Amoco locations in Chicago and Northwest Indiana. Further, the company announced it intends to provide lower sulfur gasoline in all three grades including unleaded regular in Chicago in

the spring of 2001. These fuels meet US EPA proposed sulfur requirements for year 2004 gasoline and will be available years ahead of that deadline.

For further information see http://www.bpamoco.com

…DynaMotive bio-oil technology

DynaMotive Technologies Corp (DynaMotive) announced its corporate development strategy for the year 2000 as it commences commercial exploitation of its technologies. DynaMotive aims to early position its pyrolysis technology in its key markets of Europe, Latin America, the USA and Canada in the year 2000, and plans to develop permanent presence in these markets to support expansion efforts. In 1999, DynaMotive has consistently improved the efficiency of its BioOil production technology and has met all its technical

development milestones. It is continuing to produce high grade oil from biomass and has developed engineering designs for scale up facilities. Furthermore, DynaMotive's biomass oil has been tested successfully by various engine manufacturers in Europe and Canada. For example, DynaMotive has signed an agreement with Magellan Aerospace Corp business unit Orenda Aerospace of Mississauga, Ontario, to test DynaMotive BioOil as a clean fuel to generate 'green' power in their gas turbines. DynaMotive Technologies develops and markets environmental technologies that provide clean, competitive alternatives to traditional industrial processes. The BioOil division is commercializing a renewable energy technology that converts low value forest and agricultural waste into liquid BioOil. which can be used as a clean burning liquid fuel

substitute to fossil fuels to generate green power in stationary diesel engines and gas turbines. BioOil can also be used as the raw material for a range of derivative products including fertilizers, air pollution control agents and special chemicals. For further information see http://www.dynamotive.com

…platinum-containing fuel additives

In another development, Clean Diesel Technologies has licensed the Johnson Matthey patents on 'Continuously regenerating Technology' which are based on the use of platinum-containing fuel additives in conjunction with a particulate filter.

…CARB diesel

A new cleaner-burning diesel fuel has been tested by Atlantic Richfield Co. (Arco) in the US. The tests took place one day after the federal (EPA) and Californian state (Californian Air Resources Board) regulators proposed new standards for cleaner emissions. Arco began developing cleaner gasoline for California which later served as a model for the 1996 mandated ultra-clean CARB unleaded. The adoption of CARB diesel has been credited with cleaning up the famous Los Angeles smog. There have been no emergency smog alerts this year for the first time in decades. However, the small number of diesel vehicles on the road still contribute a high proportion of the atmospheric pollution notably nitrogen oxides and par-ticulates. The new diesel fuel 'EC diesel' (EC stands for emission control) has a lower sulfur level and reduced nitrogen emissions compared to CARB diesel. Particulate emissions are 12% lower (Reuters News Service).

DuPont

…Sustainable Growth Excellence Awards

In 1999 DuPont made 12 awards of $5000 to teams of employees in the 10th annual Sustainable Growth Excellence Awards programme. The teams use the awards to make donations to external health, safety, environmental or social non-profit making organisa-tions. Winning developments have included a significant improvement in the company's ability to handle tetrafluo-roethylene, which is highly explosive and used to make a range of fluoropolymers. Other winning developments included a Brazilian teams new use for a chemicals side stream which reduced costs by $3 M and generated $5 M in revenue. In Taiwan a team developed fast clarifier technology and improved quality of plant effluent by 15%. DuPont has declared an objective of achieving 25% of revenues from non-depletable raw materials by 2010. In 1998 less than 5% of its revenues came from renewable resources. The company is investing in producing chemicals from replaceable sources such as plants and microbes. Biotechnology will be a critical enabling technology. DuPont has built a world class position in biotechnology and molecular biology which complements its three existing strengths: engineering, chemistry and information science. So far this research has focused on improving the nutritional and health qualities of food. DuPont suggests a 3-point strategy for promoting

biotechnology by chemical industry. Firstly, there needs to be an expansion of the biotechnology debate beyond the current genetically modified crops controversy. Secondly, public concerns must be addressed, and thirdly market realities and human needs must also being considered in the debate. DuPont's industrial safety business is recording growth of 20% per year.

…DuPont backs biotech

A commitment to energy conservation and the use of biotechnology has been made by DuPont. It is aiming to obtain 10% of its energy requirements from renewable resources. It is also aiming to reduce its carbon emissions by 65%. Currently, under 5% of revenues come from carbohydrates and other non-depletable resources. The company aims to increase this to 25% within 10 years. It is using biotechnology in a wide range of sectors, including the use of plants as raw materials for production of polyester. Other technologies using microbes and bioprocesses are being developed. Sales by DuPont amounted to $24.767 bn in 1998 and the company expects a small but significant proportion of sales to come from biotechnology products within five years. By the end of 1999, the company hopes to have secured a partner for its pharmaceutical operations. Although a $600 M cut in capital expenditure for nylon production in Asia was has been announced, the company is still committed to this product and also to polyester.

MTBE

The US Congress has a key opportunity now to fix a major flaw in US environ-mental policy and, starting with California, put US back on track toward cleaner air and safe drinking water, a Chevron executive told the World Fuels Conference. Patricia Woertz, president of Chevron Products Co, called for passage of a bill by Senator Diane Feinstein and Congressman Brian Bilbray which would start restoring flexibility to the rules for making reformulated gasoline and begin the process of eliminating or reducing the use of the gasoline blending chemical methyl tertiary butyl ether (MTBE).

MTBE increases the oxygen content of gasoline, and is heavily used in 16 US states to meet oxygen levels mandated by the Clean Air Act Amendments of 1990. Although MTBE is national issue in the US, the bill focuses on improving the situation first in California, where overlapping state and federal rules mean that 70% of all gasoline sold has about 10% MTBE. Woertz said the bill would be a big step toward ultimately fixing MTBE problems elsewhere by helping California refiners meet Governor Gray Davis's directive to remove it by the end of the year 2002.

…California's top air quality official has urged the US Congress not to force the State into replacing MTBE with ethanol. Michael Kenny has asked that instead they should eliminate the requirement under the 1990 Clean Air Act that all reformulated gasoline should contain 2% oxygen. This would allow California to phase out MTBE without having to increase petrol prices (Reuters News Service).

…The EPA is to take measures to substantially reduce the use in reformulated gasolines of the oxygenate MTBE which has been found to be polluting groundwater in California and elsewhere. In April 1999, the Governor of California banned the use of MTBE in gasoline sold in the state by the end of 2002 and requested the EPA to grant the state a waiver from federal oxygenate requirements for reformulated gasolines. A timetable has been set for the gradual phase-out of MTBE to give refiners time to retrofit their plants to produce gasolines which would meet air quality standards without containing MTBE. Refinery modifications will involve significant amounts of capital. No studies to date have indicated that MTBE consumption presents a health risk to humans but its distinctive odour and taste make it detectable in water even at very low concentrations and there is ample evidence of its presence in many drinking water sources, presumably as the result of leaks in underground storage tanks. The US Clean Air Act Amendments in 1990 called for the gradual introduction of reformulated gasoline (RFG) in areas which the EPA considered to have unacceptable air quality. More stringent requirements are due to take effect in Phase II beginning in 2000. By 1999, the manufacture of MTBE by oil companies and other reached 269,000 bbl/day. The EPA mandates a minimum oxygen content in fuel of 1.8% per weight which corresponds to an MTBE concentration of about 11% volume. California Air Resources Board (CARB) does not require any minimum oxygen content in summer gas but imposes a 2.7% weight limit on the grounds that high oxygen content is associated with the increased nitrogen oxide emissions, especially in summer. If MTBE use is restricted and subsequently banned, specifications for FRG could theoretically be met by substituting ethanol or other, less well-known oxygenates for MTBE or, theoretically, without the use of any oxygenates. The National Research Council (NRC) panel concluded in May that the use of both ethanol and MTBE in RFG contributed little to reducing ozone. The EPA has proposed a rule, expected to be final by the end of 1999, calling for a 90% cut in US gasoline sulfur levels nationwide by 2004. The oil industry argues that reduction should be required only in areas of the country where it will make a difference in air quality and not nationwide.

Catalysts

…maleic anhydride

Maleic anhydride catalyst capacity has been quadrupled at BP Amoco's chemical complex at Green Lake, US. The new plant is due onstream in 4th quarter 1999. The expansion was needed to meet captive demand for maleic anhydride to manufacture 1,4-butanediol using a butane-to-maleic conversion. BP Amoco has pilot plants operating which produce acrylonitrile directly from propane and ammonia. BP Amoco currently produces acrylonitrile using propylene.

…metallocene catalysts

With a 140 kg/month production facility for metallocene catalysts at Soka, Kanto Chemical is the only producer in Japan. Output is supplied to the petrochemical sector. The company is planning to increase production of the catalysts. It is also developing new catalysts, including one based on a ruthenium complex together with a small amount of strong base which is used for highly selective hydrogenation. A high yield of alcohol is obtained from ketones and aldehydes using the novel catalyst. Another new catalyst contains an optically active ligand and is capable of producing large amounts for optically active alcohol at high purity. The new catalysts do not produce significant amounts of chlorine solvent or waste metal and are therefore environmentally friendly. The company anticipates that they will be used for the production of pharmaceuticals and fine chemicals.

Brominated flame retardants

The Dead Sea Bromine Group's Flame Retardant Business unit has developed a range of non-halogenated flame retardants. The FR-20 series is based on surface-treated magnesium hydroxides and is intended for use in wire and cable applications and for nylons. The company is also undertaking research to develop its brominated flame retardants range. FR-245 [tris(tribromophenyl) cyanurate] has a bromine content of 67% and FR-1808 (brominated phenyl indane) has a bromine content of 73%. The flame retardants are environmentally-friendly and are especially effective in styrenics. FR-245 is also particularly light-stable. Both products comply with the German (Dioxin) Ordinance and EPA TSCA 40 766.25 Final Rule requirements. Dead Sea Bromine Group has raised its production capacity for FR-1025 [poly(pentabromobenzyl)acrylate] which is used as a flame retardant in engineering thermoplastics. In late 1999 it will launch the FR-300 series for PP applications. The FR-300 series is particularly suitable for flame retardant PP fibres.

Aquilo wins BOC contract for nitrogen membrane

The French gas separation equipment company Aquilo has been awarded a $3.5 M contract by BOC to supply a dozen small format membranes for the production of nitrogen from pressurized air. BOC will use these to adapt its existing nitrogen generators to the increasingly stringent requirements of customers. Nitrogen production using membranes is a low-energy, environmentally friendly process which is intended for *in situ* applications rather than for bottled gas production. The contract was negotiated in collaboration with Aquilo's parent company Whatman, UK.

Decolourable ink by Toshiba

The prospect of more attractive recycled paper, cheaper as well as whiter, could be just around the corner thanks to a new type of decolourable ink which can be made to disappear from printed paper almost as quickly as it appears. Developed by Toshiba in Japan, the new ink will help simplify paper recycling; by making the ink disappear from the paper before it is recycled, it should be possible to circumvent the energy-intensive ink removal and bleaching stages involved in conventional recycling processes. The effect of the new ink is similar to that of commercial invisible inks, but the result is a much cleaner piece of paper which is free from the acid and base residues that interfere with recycling. The ink works by reversing the chemistry of the thermal-sensitive paper used in fax machines. Fax paper is coated with a special layer containing a leuco dye and tiny capsules of a developer compound. These two components combine to produce the colour print when the paper is heated by a thermal print head in the fax machine, or when pressure is applied. Toshiba researchers are able to reverse this process by adding an eraser compound, cholic acid, to the ink formulation. To effect decolourisation, researchers either heat the paper or soak it in solvent which causes the cholic acid to lock onto the developer, breaking the hydrogen bonds attaching it to the dye. The ink costs about the same as colour toners used in copiers, and existing printing processes could be adapted to support recycling with little more than a change of ink, researchers claim.

Powder coatings

Powder coatings is generally an environmentally friendly technology offering zero VOC emissions. The greatest potential threat to health is the use of triglycidyl isocyanurate (TGIC). Until 1998 it was used as a crosslinker for exterior polyesters. The European Community has now classified it as a mutagenic, with a T(oxic) symbol. EMS Chemie has developed Primid β-hydroxy-alkylamide as a substitute for TGIC. It can produce over 70,000 tonnes/year of polyester/Primid coatings. Other contenders include Uranox aliphatic oxirane and Araldite glycidyl ester from Ciba. Polyester/TGIC continues to account for 43% of the exterior powder coating market in Europe followed by polyester/Primid with 42% and Araldite with 10%. Polyurethanes account for 24% of the global market but just 4.5% in Europe.

Making good use of young energy

According to *The Independent* (30 September 1999) a South African company has devised a clever method for exploiting the energy of children at play—a playpump which is powered by a children's roundabout. The idea is due to an Afrikaner engineer and is being used by the Playpump company run by Trevor Field. The playpump can pump 1,400 litres of water an hour compared to 150 litres an hour using a conventional hand pump. The pump is low-maintenance and provides welcome respite to the mothers of the children who can see their children's energy usefully exploited while making their own life a little easier.

Soft-touch foams

A cost-effective and environmentally friendly alternative to crosslinked PE foams has been launched by the Performance Foams Division of Dow Chemical Co for use in automotive material handling, touch-sensitive parts and military packaging. Known as Synergy Soft Touch Foams, they are made from low density polyethylene and Index ethylene-styrene interpolymers. The foams are resilient and strong. They can serve as insulators, shock absorbers and vibration dampeners. Three grades are available for use as dunnage or cushioning in packaging and as buoyancy or barrier components. Synergy Soft Touch Foams exceed industry standards for toughness and softness. The interpolymers are produced using Dow's Insite technology. Other interpolymer materials available from Dow are Quash sound management foam and Envision foam laminate. Dow's RapidRelease technology, that incorporates a patented CFC and HCFC free hydrocarbon blowing agent combined with accelerated curing systems, is used to produce the Synergy foams.

Solvent trends

…The demand for solvents has declined over the past decade due to a combination of environmental concerns and stricter legislation as well as weak European and Asian economies. The demand by 2001 is estimated at $4 bn. The trend from chlorinated solvents towards oxygenated solvents continues with the former predicted to decrease by 2.5%/year and the latter expected to increase by 2–3%/year.

…In Japan in 1998 there was a 15.1% increase in the volume of solvents recycled. About 20% of the 206,000 tonnes recycled were chlorinated compounds.

New battery technology

Exide Corp, a global leader in the business of stored electrical energy, has entered into a preliminary agreement to acquire a controlling interest in Lion Compact Energy, a privately held company conducting research in dual-graphite battery technology that could dramatically advance the search for cleaner, less expensive and more efficient batteries. Lion Compact Energy has thus far produced several prototype batteries using graphite in different forms as the electrode material. The company estimates that, in full production, its graphite battery could produce more than three times the energy of today's most advanced production batteries, with half the weight, occupying far less space, and at only one third the cost. Exide's share of Lion Compact Energy will be acquired from the Michigan Molecular Institute. Exide Corp, with revenues of about $2.4 bn/year and operations in 19 countries, is the world's largest manufacturer of automotive and industrial lead-acid batteries. For further information see http://www.exideworld.com

CFC replacements

A new unit for the manufacture of R134a (HCF 134a) has been brought on line by Xi'an Jinzhi Modern Chemical Industrial in China. R134a is a freon replacement which is currently consumed in China at a rate of 2000 tonnes/year. This is expected to rise to 5000 tonnes/year soon and new manufacturing capacity will be introduced to meet this increasing demand.

NEWS

…As the phase-out of the hydrochlorofluorocarbon foam blowing agent HCFC-141b draws close, US producers have different strategies for relacements. Elf Atochem expect to rely on existing products while AlliedSignal and LaRoche may switch to the new non-ozone depleting agent HFC-245a. This new product is likely to have a high price however, and there are also concerns over its lack of availability. Two approved alternatives are HFC-134a and saturated C3-C6 hydrocarbons (*Chemical and Engineering News*, 31 May 1999, **77**, 17).

Cleaner syntheses

…tert-butyl acetate

Lyondell Chemical has begun commercial production of *tert*-butyl acetate (TBAc) using its new, proprietary process. This process uses acetic acid and either tertiary butyl alcohol or isobutylene as feedstock, and is significantly easier and cheaper than the existing ketene-based route, and yields a purer end product. It is being carried out for Lyondell by a toll production partner in Houston, Texas. Lyondell is the first commercial producer of TBAc in the US, and is selling it at less than $1/lb. Current capacity is over 22,000 tonnes/y (50 M lbs/year) and can easily be expanded. High production costs have previously limited the availability of TBAc. The leading producer is Wacker Chemie of Germany which is thought to have a world market share of over 50%. However, Wacker's ketene process will not be able to compete with Lyondell on cost. The only other large producer is Lachema AS of the Czech Republic. TBAc's main application is as a building block for pharmaceutical compounds and as an organic synthesis reagent. It can also be used as an environmentally friendly process solvent, an application that could potentially account for large volumes and which is being targeted by Lyondell. Current world demand is about 1 M lbs/year.

…benzyl alcohol

A new method for the production of benzyl alcohol has been described. The compound which is used as a solvent in the production of dyes, fragrances, paper chemicals and pharmaceuticals is conventionally made by the hydrolysis of benzyl chloride although yields are low and the levels of by-products are high. The new method gives up to 76% product with less than 2% by-product (Xiandai Huagong, 20 May 1999, **19**, 26).

…dimethyl carbonate

A new process for the catalytic manufacture of dimethyl carbonate has been described. The reaction of carbon monoxide and oxygen in methanol can be efficiently catalysed with cobalt pyridine-2-carboxylate at a pressure of 2 MPa. This achieves a selectivity of 99% and a methanol conversion of 10.3%. The corrosion rate is believed to be less than the existing process based on copper(I) chloride catalysis.

…methanol

A new process for the production of methanol has been developed by Starchem Technologies. The new process can lead to a reduction in process costs of $50/tonne and a 25–40% reduction in capital costs. The new process is to be commercialised by Foster Wheeler under an agreement with Starchem.

Greening aircraft deicing

New jet fuel deicers which are less damaging to the environment and less harmful to humans have recently been patented by the US Navy. The compounds are acetal and ketal derivatives of glycerol. These are sufficiently soluble in jet fuels and are as effective as the current ethylene glycol-based deicers over a wide range of temperatures. At the concentrations needed to be effective for wing deicing, the current formulations are toxic and workers exposed to them have reported various health problems. Additionally the compounds can deplete rivers and streams of oxygen which can result in the death of aquatic life. (*Chemistry in Britain*, 17 October 1999).

Environmentally friendly surfactants

…The demand for non-ionic surfactants is growing and a new example of this is alkyl glycoside which is made from saccharide. This product can be used as a replacement for alkyaryl sulfonate anionic surfactants in shampoos.

…Sodium silicate can be used as a more environmentally benign replacement for phosphorus containing additives in washing powders. In China, the use of phosphorus containing washing powders was banned in 1998 and the demand for sodium silicates has grown to 500,000 tonnes/year.

…Three coconut oil soap bases for liquid cleansing applications have been developed by Concord-Chemical Company. One of these products has very light colour and low odour making it suitable for introducing dyes and fragrances.

Useful chemicals from wastes

MARS Technologies in Arizona have developed a new technology in mixed metals recovery from spent acid wastes which is an environmentally friendly alternative to deep-well disposal. Metal chlorides are absorbed by a standard ion-exchange resin, then selectively stripped by a patented method. The process has been used to recover zinc and ferrous chloride from 140 tones/month of pickle liquor in Baton Rouge, Louisiana. Zinc and a small amount of ferric salts are absorbed, then recovered. Ferrous chloride passes straight through the column and is stored for processing. In tests, the company has successfully recovered tin, copper, iron, antimony, nickel and chromium (*further information is available from Robert Bradley: bradley@marstech.com; fax +1 520 514 5161; tel +1 520 514 5160*).

High-value products from scrap tyres

The disposal of scrap tyres is a growing problem throughout the world. For example, in the European Union total scrap tyres are of the order of 2 million tonnes per year. In North America the problem is equally severe with 2.5 million tonnes produced each year with an estimated stock pile of 3000 million tyres awaiting disposal. The European Union has recognised scrap tyres as a 'priority waste stream' requiring special treatment and disposal and has recommended that a target of 65% recovery of scrap tyres should be set by the member states.

The treatment and disposal option for tyres most commonly used throughout the European Union is landfilling, however, proposed EC legislation in the form of the European Waste Landfill Directive has the specific proposal to prohibit the landfilling of whole or shredded tyres. In addition, as the costs of disposal inevitably increase illegal dumping is likely to increase. Open dumping represents a problem for local communities in

that they are an eyesore and may result in accidental fires with high pollution emissions. In addition, tyres can be a breeding ground for insects and a home for vermin.

The current disposal methods of landfilling of tyres is clearly a waste of a valuable resource and with increasing emphasis on recycling there are attempts to move the treatment of this waste stream higher up the hierarchy of waste management. Consequently alternative treatment and disposal routes for tyres are urgently being sought.

Dr Paul Williams, Reader in Environmental Engineering in the Department of Fuel and Energy at the University of Leeds, UK, has recently been awarded a £107,000 research grant from the EPSRC to undertake research into pyrolysis of scrap tyres to produce high value products. Pyrolysis is the degradation of the rubber of the tyre using heat in the absence of oxygen. The tyres rather than burn, breakdown to give an oil and gas leaving a residual solid carbon and the steel casing of the tyre. Pyrolysis of tyres therefore produces an oil, carbon and gas product, in addition to the steel cord, all of which have the potential to be recycled. The yield of oil can be up to 58 wt% of tyre and the oil has broad fuel properties similar to commercial grade light fuel oil/diesel fuel. For example, the energy value of the oil is 42 MJ kg^{-1} and sulfur content between 0.5 and 1.5 wt% depending on process conditions, and therefore the pyrolysis oils may be combusted directly or added to petroleum-derived fuels. The pyrolysis gases are composed of mainly hydrogen, methane and other hydrocarbons and have sufficient energy value that they can be used to provide the energy requirements of the pyrolysis process. The solid carbon residue left after pyrolysis has potential as a solid fuel or as a low-grade carbon black.

The EPSRC research grant has involved the design, commissioning and

Paul Williams from the University of Leeds whose new process for tyre pyrolysis could yield high-value chemicals.

Photo: Richard Moran

operation of experimental equipment in the department of Fuel and Energy at the University which uses fluidised bed and fixed bed technology to process the scrap tyres at temperatures between 450 °C and 700 °C. The scrap tyres thermally breakdown at such temperatures to produce the oils and gases and leave behind the residual carbon. The oils are condensed using a novel selective temperature condensation system, developed as part of the research grant, which concentrates the higher value aromatic chemicals as a separate fraction.

The tyre pyrolysis oil is very aromatic and contains certain chemicals in high concentration. One example is limonene, which has wide industrial application in the formulation of industrial solvents, resins and adhesives and as a feedstock for the production of fragrances and flavourings. Most importantly it is biodegradable and environmentally safe

and can be used as a replacement for CFCs. Limonene concentrations in selectively condensed fractions have reached 14% by weight in the experiments at Leeds, a concentration which can be separated using conventional processing to produce a commercially viable product. Also found in the tyre oil are indene, styrene, xylene and naphthalene all with a wide variety of industrial applications.

The research work at Leeds has produced an upgrading process for the tyre-derived carbon which produces activated carbons of similar quality to those obtainable commercially. For example, surface areas of over 600 m^2/g have been obtained in the experiments at the University. The process involves removal of the ash from the carbon using a simple acid wash procedure followed by activation at high temperatures of about 900 °C in the presence of steam or carbon dioxide. A wide variety of process parameters has been investigated to optimise the process, including activation temperature, particle grain size, the ratio of steam/carbon dioxide activation gas, activation time *etc*. The work at Leeds has also shown that the activated carbons have a porosity and sulfur content which is particularly suitable for the removal of cadmium and mercury from industrial aqueous waste-waters and flue gases.

This pyrolysis process has the potential to recycle tyres to produce high value products which make recycling not only environmentally attractive, but also *commercially* attractive.

A different approach – from Goodyear

In a different approach to the scrap tyre disposal problem, Goodyear, the world's largest tyre manufacturer, has patented a process that can efficiently devulcanise the rubber in old tyres—at least on a laboratory scale (US Patent 5 891 926). Researchers Larry Hunt and Ron Kovolac, working at Goodyear's headquarters in Akron, Ohio, USA, found that supercritical 2-butanol (150–300 °C, 1000–1500 psi) exhibited the right solvation properties to extract natural rubber from the vulcanised product. The process breaks the carbon–sulfur and sulfur–sulfur crosslinks formed during the vulcanisation process, separating the rubber molecules from the oil, carbon black and sulfur present in the tyre compound. The extracted rubber is almost identical to virgin rubber, and can therefore be cured and used to make new products, but it remains to be seen if the process can be scaled-up successfully to provide a viable alternative to landfill disposal.

Clean polymer synthesis and processing using scCO$_2$

Andrew Cooper from Liverpool University in the UK describes how scCO$_2$ (supercritical carbon dioxide) is proving to be a valuable green alternative to conventional solvents in polymer synthesis and processing

Concern over volatile organic solvent emissions and the generation of aqueous waste streams has prompted a number of chemists and chemical engineers to seek new, cleaner methods for polymer synthesis[1] and polymer processing.[2] The use of supercritical carbon dioxide (scCO$_2$) has attracted particular attention in both of these areas for the following reasons:

● CO$_2$ is non-toxic, non-flammable, chemically inert, and inexpensive
● Supercritical conditions are easily obtained: T_c (CO$_2$) = 31.1°C; P_c, (CO$_2$) = 73.8 bar (Figure 1)
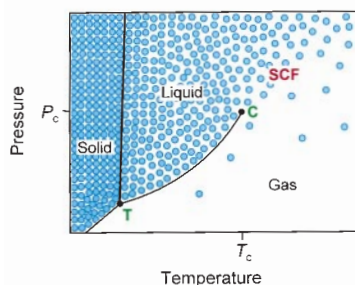
Figure 1 Schematic phase diagram for CO$_2$ showing the supercritical region

● The solvent may be removed by simple depressurisation
● The density of the solvent can be 'tuned' by varying the pressure
● Many polymers become highly swollen and plasticised in the presence of CO$_2$

On the other hand, the use of supercritical fluids requires elevated pressures and relatively specialised equipment, and these considerations must be balanced carefully with the perceived advantages for a given application. However, there are many recent examples which suggest that the benefits of using CO$_2$ as an alternative solvent might warrant the

additional complexity associated with supercritical fluid technology, at least for certain applications. The aim of this article is to highlight some of these areas.[3]

Polymer synthesis

Much of the pioneering work in the field of polymer synthesis using scCO$_2$ has been carried out by Professor J. M. DeSimone and colleagues at the University of North Carolina at Chapel Hill (UNC), USA.[4] In 1992, this group showed that it was possible to synthesise amorphous fluoropolymers in CO$_2$ under relatively mild conditions by homogeneous solution polymerisation.[5] Since the only other solvents for these polymers tend to be chlorofluorocarbons (CFCs), the use of CO$_2$ represents a much cleaner route to materials of this type. However, with the exception of certain amorphous fluoropolymers and polysiloxanes, the vast majority of polymers show negligible solubility in CO$_2$ under practicable conditions (<100 °C, <100 bar). Hence, a number of research groups have studied the synthesis of polymers by heterogeneous polymerisation in scCO$_2$ (*i.e.*, under conditions where the resulting polymer is not soluble in the supercritical solvent). In 1994, DeSimone demonstrated that it was possible to synthesise polymers such as poly(methyl methacrylate) (PMMA) in CO$_2$ by dispersion polymerisation using specially designed, CO$_2$-soluble surfactants.[6] Since dispersion polymerisation is usually carried out in solvents such as hydrocarbons or C$_1$–C$_5$ alcohols, the use of CO$_2$ has potential to reduce organic solvent usage. These techniques have recently been extended to the synthesis of a range of materials, including water-dispersible polymer powders[7] and well-defined cross-linked microspheres (Figure 2).[8] Water-dispersible powders are useful because they can be transported dry, thus saving on transport costs, while cross-linked microspheres are

very important in applications such as chromatographic separations and polymer-supported synthesis.

The use of scCO$_2$ for the synthesis of porous polymers is an area of great interest, particularly since conventional processes tend to be solvent intensive and can generate materials containing organic solvent residues which may be difficult to remove. Carbon dioxide has allowed the 'solvent-free' preparation of polymeric materials with pore sizes spanning a very broad range, from microcellular foams down to macroporous resins (Figure 3) and mesoporous/microporous aerogels.[9]

In the UK, several academics are investigating aspects of the use of CO$_2$ for polymer synthesis, including groups in Nottingham, Cambridge, and Liverpool.[10]

Polymer processing

Carbon dioxide has been used in a wide range of polymer processing applications, the most established of which are polymer fractionation and extraction.[11] Both of these techniques exploit the variable density which is associated with supercritical fluid solvents. More recently, there has been much interest n the use of CO$_2$ for the infusion or 'impregnation' of molecules into
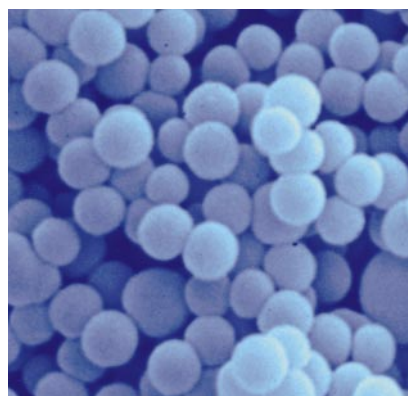
Figure 2 Cross-linked polymer microspheres synthesised in scCO$_2$, average diameter = 410 nm, see ref. 8
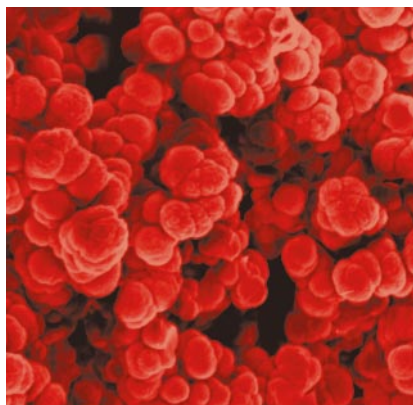
Figure 3 Internal structure of a porous polymer monolith synthesised using scCO$_2$, average pore size = 7.8 μm, see ref. 9(b)

polymeric materials. From an environmental perspective, a particularly exciting technique is disperse dyeing using scCO$_2$.[12] In this approach, the dye molecule has very low solubility in CO$_2$ (*e.g.*, mole fractions of $10^{-5}–10^{-6}$) However, because the dye molecules partition preferentially into the polymer phase, significant quantities of dye can be loaded into the polymer in a relatively short period.[13] In addition to using a clean solvent, very little dye is actually dissolved in the fluid at any given time, thus minimising dye loss and environmental burdens.

Another exciting processing technique is the Vedoc Advanced Materials Process or 'VAMP®', which was recently

Biography

Andrew Cooper obtained his PhD at the University of Nottingham, working with Professor Martyn Poliakoff in the area of organometallic chemistry. He then spent two years (1995–1997) as an 1851 Research Fellow at the University of North Carolina at Chapel Hill, USA, working with Professor Joseph DeSimone on the development of novel dendritic surfactants for extractions using CO$_2$ as the solvent (Cooper *et al.*, Nature, 1997, 389, 368). From 1997 to 1999, he held a Ramsay Memorial Research Fellowship at the Melville Laboratory for Polymer Synthesis in Cambridge, UK, working with Professor Andrew Holmes on polymer synthesis using supercritical CO$_2$ (Cooper *et al.*, Macromolecules, 1999, 32, 2156). He was appointed as a Royal Society University Research Fellow at the University of Liverpool, UK, in January 1999.

commercialised by Ferro Corporation (Cleveland, OH).[14] This process utilises the fact that CO$_2$ is a good plasticising agent (*i.e.*, it can cause polymers to soften and flow, even at low temperatures). The method has been applied successfully to low-temperature processing of a range of composite materials, particularly polymer–pigment formulations for use as powder coatings. Other important methods for polymer particle formation include rapid expansion from supercritical solutions (RESS) and a range of antisolvent precipitation techniques.[15] Supercritical CO$_2$ has also been exploited for the solvent-free application of protective fluorinated coatings[16] and for dry-cleaning,[17] the latter of which has already shown real commercial promise.

Finally, carbon dioxide has been viewed as a potential solvent for microlithography. At present, the semiconductor industry produces millions of gallons of organic and aqueous waste effluent every year, all of which requires treatment. Supercritical solvents offer the possibility of simpler separations and recycling, and new processes are under evaluation which use CO$_2$ as the solvent, both in the spin-coating stage and also in the development step.[18]

Conclusions

Carbon dioxide has great potential as an alternative solvent for polymer synthesis and processing. The drive to use CO$_2$ is especially strong in the case of processes which use volatile organic solvents. However, there may also be cases where CO$_2$ is a viable substitute in aqueous processes, particularly if separations are simplified by the use of a supercritical solvent. A major breakthrough in the acceptance of this technology would be the generation of novel polymeric materials that are difficult or even impossible to obtain without the use of supercritical fluids. Whilst this may be a challenging goal, the rapid growth of this area over the last few years suggests that we will see future developments in the use of CO$_2$ for the synthesis and processing of progressively more advanced materials.

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Eco-labelling for domestic products

Which magazine has published its findings from a review of eco-labelling schemes for domestic products. In 1998, the UK Government launched a voluntary code of practice—the Green Claims Code—to give guidance to manufacturers wishing to make green claims about their products. It was hoped that the code would help to avoid confusing logos and misleading statements and claims, and enable consumers to better judge the relative environmental merits of different products. The verdicts on some of the schemes are summarised below.

The Forest Stewardship Council (FSC)

This was set up in 1993 and is meant to show which wood-based products come from well-managed forests and cause minimal environmental and local community damage. *Which* found this to be an example of a good environmental- labelling scheme with clear objectives, focused targets and thorough monitoring.

Volatile organic compounds (VOCs).

This was developed by the B&Q stores and was meant to inform customers of the level of VOCs in paints and varnishes. Not all manufacturers have adopted the scheme. *Which* view this as an important scheme and suggest that it can be improved through independent tests and more consistent reporting of information by the various manufacturers.

Washright.

This was launched in 1998 and is part of a campaign by the European soap and detergent manufacturer's trade association to reduce the environmental impact of laundry detergents by 2002. This scheme is meant to educate users about the correct quantity of detergent that should be used and to reduce the energy consumed per application. All UK laundry-detergent manufacturers are taking part in this voluntary scheme. *Which* found that not all manufacturers gave clear information and some simply refer the customer to a web site.

Which also reported on the failure of the eco-labelling scheme. This was launched by the EU in 1992 with the aim to endorse products that cause less damage to the environment during their use or production.

Unfortunately take-up of the scheme has been very slow with only about 200 products having been awarded. This lack of popularity is at least partly due to the high fees as well as to competition with local environmental schemes.

The scheme is currently being revised.

Which also revealed some remaining examples of unhelpful and misleading green logos and statements on packaging. These include:

- claims on aerosol products to be 'CFC-free' even though CFCs have not been used in consumer aerosols for 10 years
- claims on washing powders that they contain biodegradable detergents when all such materials must be biodegradable by law
- claims on paint products that they have 'no added lead' when its been illegal to add lead to paint for 10 years

Which, October 1999

DOE support for alternative fuels

The US Department of Energy (DOE) has awarded a $4.2M grant towards a $5.4M research project on the production of cleaner alternative fuels and premium-quality chemicals. This project is backed the Consortium for Fossil Fuel Liquefaction Science (CFFLS)— a five-University partnership (University of Kentucky, University of Pittsburgh, University of Utah, West Virginia University, Auburn University) engaged in a broad research program to liquefy waste material with coal to transform a major environmental disposal problem into a valuable transportation fuel

resource. Specific projects under the DOE grant will include new methods of using coal, coke, municipal waste and natural gas along with unconventional chemical processes (*Oil and Gas*, 1999, **97**, 4). For more information on the CFFLS see http://www.uky.edu/CFFLS/

Tougher pollution legislation

The EPA in Washington is to introduce tougher new legislation on emissions form trucks. Details are to be expected within weeks. Environmentalists have claimed that 26% of the smog-causing nitrogen oxides are emitted from larger trucks even though they only represent 2.5% of all vehicles on the US roads. Earlier this year, the EPA proposed to sharply cut smog-causing chemicals found in automobiles as well as new requirements for low-sulfur gasoline across the USA. The tougher emissions and fuel standards for large trucks will begin to be phased in by 2007 (Reuters News Service).

Germany pushes for sulfur-free diesel

Germany has urged the EU to introduce sulfur-free diesel by 2007. They believe that the 1998 agreement to reduce the sulfur levels to 50 ppm did not go far enough. It called for fuels with less than 10 ppm sulfur to be available from 2005 and mandatory by 2007. Reduced sulfur levels will have multiple benefits including increased lifetimes for catalytic converters, reduced fuel consumption, and reduced emissions. Germany will offer tax incentives for sulfur-free fuels from January 2003 (Reuters News Service).

Greening the HSE

One of the major considerations of the Environmental Audit being carried out by the Health and Safety Executive (HSE) has been the UK Government's initiative to green its departments. Following this the 'Green Team' was launched in July 1999 with responsibilities to create and monitor a programme for improving the environmental impact of HSE's operations and leading all relevant HSE

FORUM

initiatives. Initially they are expected to produce a Green Improvement Programme which will include conserving resources such as water, energy, etc and minimising waste. The HSE also wants a network of green contacts to be established throughout the HSE (http://www.open.gov.uk/hse/hsehome.htm).

Green Chemistry Network concentrates on education

In recent months the Green Chemistry Network (GCN) has started to concentrate more effort to get green chemistry concepts into schools. We have been working with the editorial board of *Chemistry Review* (Philip Allan Publishers, ISSN 0959 8464) to provide a variety or articles covering many aspects of green chemistry. Green chemistry will be the theme running throughout volume 9 of the journal; issues 1 and 2 gives an overview of the subject together with more detailed articles on how catalysis can improve atom economy, the search for eco-friendly electroplating electrolytes and green chemistry resources available on the web. We are also becoming increasingly involved in RSC's Chemistry at Work events, about 70 GCSE pupils from six schools in North Yorkshire attended a recent event at York. The level of understanding they demonstrated about green issues was high and they were particularly interested in what industry is doing to become greener.

We are also involved in running a schools challenge (along with ACTIN) on the uses of renewable resources as chemical feedstocks. This is part of a wider Food and Farming Challenge run by the Yorkshire Agricultural Society as an annual event and involves 14–18 year olds researching and presenting a report on a scientific issue connected with agriculture.

The RSC's Environmental Chemistry Group, the RSC's Education Division and the GCN are planning a one-day con-ference/ training course for teachers and lecturers on green chemistry and environmental sciences relevant to the curriculum. This event will be held in London on 25 March 2000.

Joe Breen Memorial Scholarship

Letter from Dennis Hjeresen, Acting Director of the Green Chemistry Institute

Following the sad passing of Joe Breen, one of the fathers of green chemistry this past summer, a Joe Breen Memorial Scholarship was established. The current fund stands at about $2200 and the American Chemical Society has generously offered to match the fund, if it exceeds $2500. Thus, I am requesting additional donations to enable the matching sum to be exceeded. Information will be released shortly on how to apply for scholarship funding and the necessary criteria, but it is intended that the funds will be directed to an educational activity—very much in the spirit of Joe Breen.

Donations should be sent to:
*The Green Chemistry Institute
Internship Program,
The Green Chemistry Institute,
600 Barranca Road,
Los Alamos, NM 87544,
USA*

Thanks,

Dennis L. Hjeresen
Los Alamos National Laboratory
e-mail: dennish@lanl.gov

Know of any green chemistry activities?

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

FOCUS ON...

Separation processes at Loughborough University

Mike Lancaster looks at the separation process research being carried out at Loughborough, UK, with emphasis on the membrane work of Professor Richard Wakeman and colleagues

Professor Richard Wakeman

Most chemists, by training, focus on the chemical reaction, maximising yield and raw material utilisation. Green chemistry however needs to take account of post reaction processes such as product isolation, purification and recycling of non-product streams. In these areas the scope for the traditional chemist to make an impact is often limited and it is left to the chemical engineer to drive towards cleaner technology. The Chemical Engineering Department at Loughborough University is particularly strong in the area of separation processes, both physical (*e.g.* gas or liquid filtration and membrane processes) and chemical (*e.g.* using ion exchange resins to remove toxic metals).

Professor R. J. Wakeman obtained his B.Sc. and Ph.D. from UMIST and spent a short period in industry with Lennig Chemicals before embarking on his academic career. Before taking up his current position at Loughborough in 1995 he spent time at UMIST and Exeter. He is currently chair of the European Federation of Chemical Engineers working party on Filtration and Separation.

Crossflow membrane microfiltration is currently one of Richard Wakeman's main areas of interest. This separation process is particularly useful for removal of dispersed materials in the size range 0.05 to 10 microns from a liquid steam by forcing the liquid through a porous membrane. In crossflow filtration the dispersion flows tangentially to the membrane surface, this flow generates forces which tend to remove the deposited layers from the membrane surface thus helping to keep the membrane clean and lengthening the time between cleaning procedures and membrane replacement.

Because of this, crossflow microfiltration is particularly useful for continuous processes.

Microfiltration is the oldest of the membrane separation technologies but its industrial implementation has been much slower than expected; to a considerable extent this is due to the initial rapid decline in permeate flux. Wakeman has spent much time looking at the cause and potential solutions to this problem, some of the conclusions are shown in Table 1.

Potential industrial applications

One method for reducing cake formation and fouling and hence increasing the flux rate is to apply an additional force field such as direct current or acoustic fields to the membrane. The effect of the electric field is to alter the direction of the particle such that it does not approach the membrane surface. Wakeman has used this technique in the development of technology for the microfiltration (through tubular ceramic membranes) of titanium dioxide dispersions, a frequent problem for the paint and coatings industries. For

example dilute dispersions of titanium dioxide in sulfuric acid may readily be concentrated from 2% to 60%. Wakeman's long-term aim is to develop a process using a.c. as this will be much safer to use on an industrial scale than the present d.c. technology.

A problem often encountered by biotechnology companies concerns concentration of solutions containing small amounts of protein, Wakeman has demonstrated that electrically enhanced microfiltration technology is highly suited to this application, however there is a limit to the electrical potential that can be used due to localised heating which may cause degradation of the protein structure. However the technology has advantages over centrifuges which are commonly used for this process since the high shear associated with centrifuges also lead to protein degradation. Electrical enhancement of membrane filtration processes is highly efficient leading to smaller more versatile filtration equipment.

Table 1 Some parameters effecting flux decline in crossflow microfiltration

Parameter	Effect
Crossflow velocity	Increase in crossflow velocity increase flux for systems containing high amounts of particle fines
Filtration pressure	High pressures lead to higher fluxes for systems containing large particles (over 24 micron)
Membrane wettability	Hydrophobic membranes have higher initial fluxes than hydrophilic one - but they even out with time
Membrane morphology	This has an effect when a small fraction of fines are present in a low concentration suspension

FOCUS ON...

Use of acoustics to prevent fouling is useful for dispersions containing fine particles suspended at around 1000 ppm where normal filtration rates are low. Ultrasound behaves in a similar way to electric fields, changing the particles trajectory. Using this technique it is possible to increase the concentration of particles by 50% per pass. This is of current interest to water companies for removal of hydrocarbon pollutants, although the volumes involved are too great for ultrasound to be used commercially at present.

Professor Wakeman has used his membrane expertise to assess methods of removing pollutants from both waste-water and in process effluent streams, with the duel aim of producing clean water and recovering the pollutants for reuse. One particular area he has studied is removal of latex particles, widely used in paints and adhesive formulations and frequently found at the 1% level in discharges from manufacturing processes. To make re-use economical these particles need to be concentrated up to around 30%. This has been shown to be viable by use of flocculants such as acrylic acid / fatty ester copolymers to prevent the latex particles blocking the membrane pores. Other applications Wakeman's group have worked on include the pilot scale separation of different types of surfactant from process waste streams. If small units are fitted to the end of each manufacturing plant this technology has potential for significantly reducing the amount of surfactant waste leaving the factory.

Separation of oil-in-water emulsions

Dr Iain Cumming along with Dr Richard Holdich have been applying novel membrane technology to a problem common to many industries that of breaking oil-in-water emulsions. Oil-in-water emulsions are produced in large volumes during offshore oil production, from metal working and during food manufacture, although membranes have been used for breaking these emulsions the process has never been very efficient. The Loughborough team discovered that this was largely due to the way membranes are manufactured. Normal membranes do not have straight through pores instead the channels are interwoven and the separation is via depth filtration. Excellent results have been obtained by using straight through metallic tubular crossflow membrane filters, giving oil rejections up to 97%.

Cumming, in co-operation with Dr

Klaus Hellgardt is about to begin work on a new research topic, which could provide a safe, simple and clean alternative to many oxidation processes. They are working on membranes whose oxygen permeability is controlled by an electric current. A tubular membrane reactor is envisaged in which the inner membrane surface is coated with catalyst, hydro-carbons are pumped into the tube and oxygen (from air) enters through the membrane in a controlled manner by manipulation of the electric current. Hence the oxidation process can be easily carried out outside the flammability limits using air as the oxidant source. There is some precedent for such membranes, in the US Air Products have started to use similar membranes for separating oxygen from air in place of cryogenics.

Chemical separation processes

As well as all the research into physical separation processes there is a significant amount of work being carried out at Loughborough on chemical separations including adsorption of trace toxic metals and organic pollutants from aqueous streams using, for example, ion exchange resins and hypercrosslinked polymers. Leading this work is Head of Department Professor Michael Streat.

Streat has been working with the metal plating industry for some time to identify simple, inexpensive solutions to help the many small companies involved clean up their effluent. Much of this work has centred on the use of novel chelating ion exchange resins containing aminophosphonate or amidoxime type groups to remove pollutants such as Cu, Ni, Zn, Co, Cr and Cd ions from plating effluent streams. More recently the group has demonstrated the benefits of using seaweed for this purpose. This work, carried out under the EU Brite-Euram project and trialed in Finland has shown that it is the carboxylate groups present on the seaweed which are vital for activity. In many cases treated seaweed has outperformed commercial ion exchange resins.

Further work by Streat's group at reducing the cost of separation processes, making them more accessible to smaller companies is aimed at producing activated carbon from renewable waste sources. Potential sources of this carbon include waste sugar beat and straw. The main focus of the work is centred on optimising the carbonisation process to produce carbon with the correct physical form, porosity and surface area. It is expected that carbon suitable for both removal of toxic metals and trace organic pollutants such as pesticide residues will be produced.

Reactive distillation

One of Professor Streat's leading co-workers over recent years is Dr Basu Saha who has recently been appointed to a lectureship at Loughborough. Dr Saha is currently establishing his own 'Green Chemistry' research programmes in the area of reactive distillation.

Reactive distillation has received considerable attention in recent years as an advance over conventional processes where the conversion is limited by unfavourable chemical equilibrium. The main advantages of this process, relative to conventional alternatives are the possibility of carrying out equilibrium limited reactions to completion and simultaneous removal of the product from the reaction mixture in a single unit, which in turn reduces reactor and recycle cost. Ion exchange resins also find application in reactive distillation columns where they play the dual role of catalyst as well as tower packings.

In recent years, reactive distillation has been considered for the important anti-knock compound MTBE and for the manufacture of high purity methyl acetate. The conversion of formic acid, in aqueous solutions, to cyclohexyl formate by reaction with cyclohexene, in a reactive distillation column packed with an acidic ion exchange resin catalyst has been studied by Saha. A favourable comparison between the rate of esterification in batch mode and in a reactive distillation column was made.

Other processes Dr Saha will be studying include recovery of dilute acetic acid solution by esterification with alcohols and various trans-esterification processes.

Further reading

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Green Chemistry Challenge Award presented to Terrence J Collins

More 1999 Presidential Green Chemistry Awards

Paul Anastas, Mary Kirchchoff and Tracy Williamson of the US EPA present the last in a series of short profiles on this year's Presidential Green Chemistry Awards.

To Terrence J. Collins, Carnegie Mellon University for the development TAML™ Oxidant Activators used in general activation of hydrogen peroxide for green oxidation technologies.

In nature, selectivity is achieved through complex mechanisms using a limited set of elements available in the environment. In the laboratory, chemists prefer a simpler design that utilizes the full range of the periodic table. The problem of persistent pollutants in the environment can be minimized by employing reagents and processes that mimic those found in nature. By developing a series of activators effective with the natural oxidant hydrogen peroxide, Professor Terry Collins has devised an environmentally-benign oxidation technique with widespread applications. TAML™ activators (tetraamido-macro-cyclic ligand activators) are iron-based and contain no toxic functional groups. These activators offer significant technology breakthroughs in the pulp and paper industry and the laundry field.

The key to quality papermaking is the selective removal of lignin from the white fibrous polysaccharides, cellulose, and hemicellulose. Wood-pulp delignification has traditionally relied on chlorine-based processes that produce chlorinated pollutants. Collins has demonstrated that TAML™ activators effectively catalyze hydrogen peroxide in the selective delignification of wood pulp. This is the first low-temperature peroxide oxidation technique for treating wood pulp, which translates to energy savings for the industry. Environmental compliance costs may be expected to decrease with this new approach because chlorinated organics are not generated in this totally chlorine free process.

TAML™ activators may also be applied to the laundry field, where most bleaches are based on peroxide. When bound to fabric, most commercial dyes are unaffected by the TAML™-activated peroxide. However, random dye molecules that 'escape' the fabric during laundering are intercepted and destroyed by the activated peroxide before they have a chance to transfer to other articles of clothing. This technology prevents dye-transfer accidents while offering improved stain-removal capabilities. Washing machines that require less water will be practical when the possibility of dye-transfer is eliminated.

An active area of investigation is the use of TAML™ peroxide activators for water disinfection. Ideally, the activators would first kill pathogens in the water sample, then destroy themselves in the presence of a small excess of peroxide. This protocol could have global applications, from developing nations to individual households.

Potent oxidation catalysts

Submicromolar quantities of Carnegie Mellon's easily made tetraamido-macrocyclic ligand (TAML™) catalysts activate peroxide at low temperature to perform very selective oxidation chemistry in diverse fields-of-use.

A TAML™ catalyst

plus

PULP AND PAPER
pulp delignification and effluent decolorization

TEXTILES
dye bleaching and effluent decolorization

LAUNDRY
dye transfer inhibition and stain bleaching

WATER CLEANING
halogenated aromatics and organics destruction
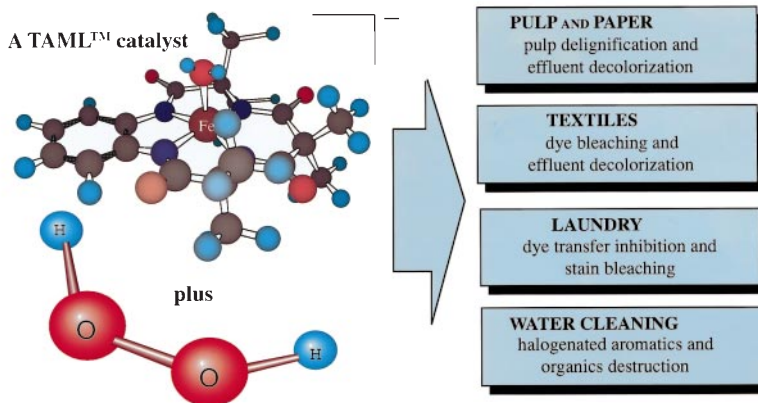
The versatility of the TAML™ activators in catalyzing peroxide has been demonstrated in the pulp and paper and laundry industries. Environmental benefits include decreased energy requirements, elimination of chlorinated organics from the waste stream, and decreased water usage. The development of new activators and new technologies will provide environmental advantages in future applications.

To Lilly Research Laboratories for their practical application of a biocatalyst in pharmaceutical manufacturing

The synthesis of a pharmaceutical agent is frequently accompanied by the generation of a large amount of waste. This should not be surprising, as numerous steps are commonly necessary, each of which may require feedstocks, reagents, solvents, and separation agents. Lilly Research Laboratories has redesigned its synthesis of an anticonvulsant drug candidate, LY300164. This pharmaceutical agent is being developed for the treatment of epilepsy and neurodegenerative disorders.

The synthesis used to support clinical development of the drug candidate proved to be an economically viable process, although several steps proved problematic. A large amount of chromium waste was generated, an additional activation step was required, and the overall process required a large volume of solvent. Significant environmental improvements were realized upon implementing the new synthetic strategy. Roughly 34,000 liters of solvent and 300 kg of chromium waste were eliminated for every 100 kg of LY300164 produced. Only three of the six intermediates generated were isolated, limiting worker exposure and decreasing processing costs. The synthetic scheme proved more efficient as well, with percent yield climbing from 16% to 55%.

The new synthesis begins with the biocatalytic reduction of a ketone to an optically pure alcohol. The yeast *Zygosaccharomyces rouxii* demonstrated good reductase activity, but was sensitive to high product concentrations. To circumvent this problem, a novel three-phase reaction design was employed. The starting ketone was charged to an aqueous slurry containing a polymeric resin, buffer, and glucose, with most of the ketone adsorbed on the surface of the resin. The yeast reacted with the equilibrium concentration of ketone remaining in the aqueous phase. The resulting product was adsorbed onto the surface of the resin, simplifying product recovery. All of the organic reaction components were removed from the aqueous waste stream, permitting the use of conventional wastewater treatments.

A second key step in the synthesis was selective oxidation to eliminate the unproductive redox cycle present in the original route. The reaction was carried out using dimethylsulfoxide, sodium hydroxide, and compressed air, eliminating the use of chromium oxide, a possible carcinogen, and preventing the generation of chromium waste.

The new protocol was developed by combining innovations from chemistry, microbiology, and engineering. Minimizing the number of changes to the oxidation state improved the efficiency of the process while reducing the amount of waste generated. The alternative synthesis presents a novel strategy for producing 5*H*-2,3-benzodiazepines. The approach is general and has been applied to the production of other anticonvulsant drug candidates. The technology is low cost and easily implemented and should have broad applications within the manufacturing sector.

Chemistry Awards

Following the success of these Presidential Green Chemistry Awards in the USA, awards for Green Chemistry have been established in the UK, supported by The Royal Society of Chemistry (RSC), Salters' Company, the Jerwood Foundation, Department of Trade and Industry (DTI) and Department of the Environment, Transport and the Regions (DETR).

The awards are designed to encourage more people to engage in Green Chemistry research, promote recent developments by industry and encourage sharing of best practice. Awards will be made both for academic research and commercial development by industry of Green Chemical Technology.

Full details of the awards were published in the October issue of Green Chemistry and further information can be obtained from Mike Lancaster [email: greennet@york.ac.uk, Tel: (01904) 434549, Fax: (01904) 434550]. Administration will be carried out by the Green Chemistry Network at the University of York with an expert panel appointed by the RSC and Salters' judging the nominations. The first of these annual awards will be made next year with nominations closing 31 March 2000.

FEATURE

On the efficiency and sustainability of the process industry

P. Hinderink of the Process Design Center in Breda, and H. J. van der Kooi and J. de Swaan Arons, both from the Laboratory of Applied Thermodynamics and Phase Equilibria at the Delft University of Technology (all in The Netherlands) explore the use of the thermodynamic concept of lost work for discussing the sustainability of the process industry.

Introduction

The process industry is a large consumer of raw materials, which are utilised both as feedstock for its numerous products and as energy source to drive its numerous processes. In the scope of sustainable development, consensus on the limited availability of our natural resources, and on the need for closed cycles in our ecosphere has grown. Hence, the current approach of our process industry is in question.

One might raise the question 'how sustainable are we?' In answering this question, first, we have to fall back to the efficiency question. There is a need for quantitative figures on the efficiency with which natural resources are consumed. Such quantitative figures can be provided by the known thermodynamic concept of lost work, indicating the discrepancy between the ideal thermodynamic situation and our current process technology. This paper is partly based on the work presented by Hinderink *et al.* (1996a).

Lost work in the process industry

Lost work analysis has so far drawn the most attention in the energy-systems area, where heat is converted to power or electricity. It has less penetrated into the chemical process industry, perhaps because of its greater complexity.

Work-potential of materials (chemical exergy)

The theoretical work-potential of an energy-source depends on the extent to which it deviates from equilibrium with its natural surrounding. When heat and material streams are ideally brought in equilibrium with their surroundings, a maximum amount of work is available, which is often called 'exergy'. If such an equilibration is not carried out ideally—which is always the case for real processes—a less than maximum amount of work is available, the remainder being lost, *i.e.* lost work. The precise calculation of the work-potential of material streams has been described by Szargut *et al.* (1988), and Hinderink *et al.* (1996b).

Lost-work analysis (exergy analysis)

In real material conversion processes, primary materials (natural resources) are converted to consumer materials and heat. These processes do not proceed ideally, so part of the work-potential of the primary materials will be lost.

To obtain a 'feeling' for lost work in the process industry, the production processes of several 'large-quantity' products have been analysed. This paper only focuses on input and output streams of the conversion process; production of the natural resources, transportation, and storage, are excluded from the system boundary, because most often the largest part of lost work is occurred in the conversion step. Elaborate lost work analyses are given, for example, by Hinderink *et al.* (1996c) and Wall (1988). Figure 1 illustrates the general result of a lost-work analysis of a material conversion process in a so-called Grassmann
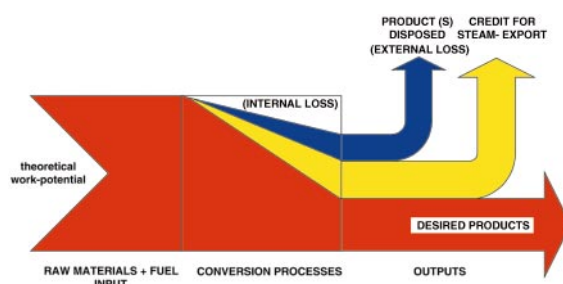
Figure 1 Generic Grassmann diagram for a material and energy conversion process.

diagram. A lost work analysis reveals internal losses due to process imperfections, whereas an energy analysis has to ascribe losses to waste material and heat streams leaving the process (*i.e.*, physical streams).

The input-side of such a process is represented by natural resources (primary resources). No distinction has been made between resources used as feedstock and resources applied as fuel; they all are quantified by their theoretical work-potential, the universal measure. The output-side is represented by the theoretical work-potential of the desired product(s) and of recovered useful heat (in the form of a steam credit).

By comparing the total amount of work-potential entering and leaving the process, the loss of work-potential is revealed, which is either due to process-inefficiencies or material/heat release to the environment, so internal and external losses are lumped. All data have been taken from published literature (Table 1).
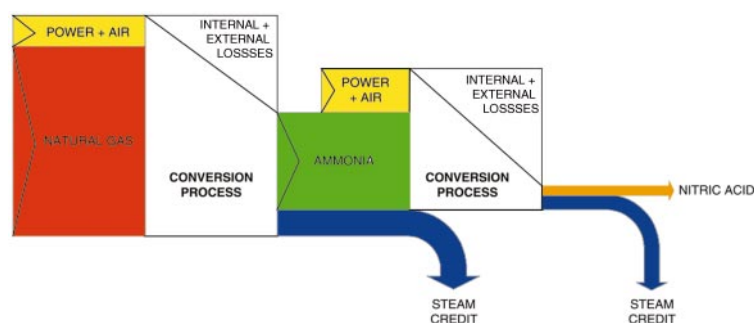
Figure 2 Simplified Grassmann diagram for the nitric acid process

The processes

Table 1 gives a 'thermodynamic blueprint' of some large-scale production processes. The numerical values presented refer to the technology level of the 1970s or 1980s and are based on primary (natural) resources only, *e.g.* natural gas and air. Because only primary resources are allowed to enter the processes, several sub-processes can be present inside the system, *e.g.* for the generation of intermediate products, or for the generation of steam or electricity. Lost work involved with the latter type of sub-processes is handled by using commonly applied second law-efficiencies (*e.g.* 50% for power production *via* cogeneration).

An example of a process with an intermediate product is the urea process. The second step, starting from ammonia, is over 90% efficient, whereas the total process—thus having ammonia just as an intermediate product—shows an efficiency of only half of this value. For the nitric acid process, the second step is the least efficient as indicated by the simplified Grassmann diagram in Figure 2.

The left-hand box overleaf gives the calculation procedure for the theoretic work-potential of natural gas. The right-hand box overleaf presents the lost-work analysis for the production of hydrogen from natural gas via the steam reforming route.
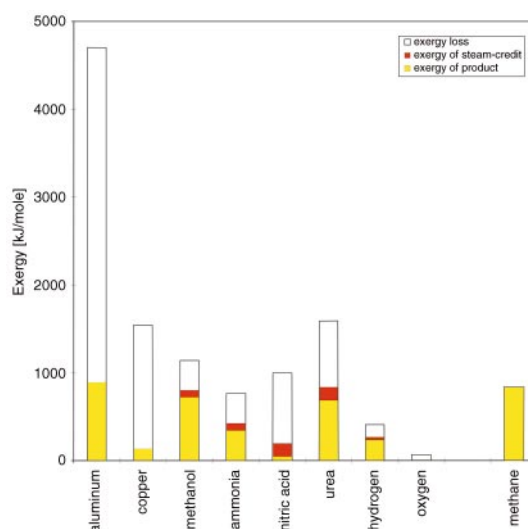
Figure 3 Graphical representation of the lost work analyses.

Results of lost-work analyses strongly depend on the system boundary considered and the credit that is given to co-products and by-products. Therefore, the analysis results can vary per author.

Thermodynamic efficiency

Although efficiency-values can be misleading because they can be defined in numerous ways (Wall, 1977; Gong and Wall, 1997), they are easy to handle. The definition of thermodynamic efficiency applied here is the ratio between work-potential of the desired products (excluding useful heat) and the primary resources applied. Usually, thermodynamic efficiencies based on lost-work analysis do not exceed 70% when starting from primary resources. At the higher side of the efficiency-range, the production of organic products can be found, while inorganic and metallurgical processes are at the lower side of the efficiency range. A combination of low efficiency and high input of work-potential indicates the need for process improvement. An overview of absolute lost work figures for the process industry, *e.g.* as shown in Figure 3, is more distinct and can be of use to determine which products and/or which processes need to be reconsidered in view of sustainable development.

Table 1 Results of global lost work analyses of several important production processes

Final product	Molecular weight	Raw materials	Data taken from	Technology level	Thoretical work-potential [kJ/mol final product]				
					Raw materials	Final product	Steam credit	Lost work	thermodynamic efficiency * [%]
hydrogen	2	natural gas/air	Giacobbe *et al.*	1990	409	236	28	145	58
ammonia	17	natural gas/air	Cremer	1980	763	338	85	340	44
aluminum	27	bauxite	Szargut; Habersatter	1990	4703	888	n.a.	3815	19
methanol	32	natural gas/air	Supp	1985	1136	717	80	339	63
oxygen	32	air	Ullmann	1980	64	4	n.a.	60	6
urea	60	natural gas/air via ammonia	Cremer; Pagani	1980	1590	686	150	754	43
nitric acid	63	natural gas/air via ammonia	Cremer; Lowenheim *et.al.*	1975	995	43	151	801	4
copper	63.5	copper ore	Szargut; Boustead	1980	1537	130	n.a.	1407	9
methane	16				830				

*) excluding steam-credit

FEATURE

Figure 4 shows lost work figures for the utilisation of natural gas for various purposes
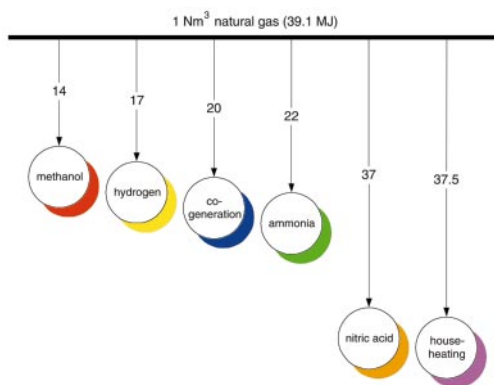
Figure 4 Lost work figures for the utilisation of natural gas for various purposes

Table 2 A typical composition and the chemical work-potential of Dutch natural gas

Component	Composition mole%	Chemical work-potential *) [kJ/mole]	Contribution [kJ/mole]
methane	90	830	747
ethane	8	1496	120
nitrogen	1.5	0.7	0.01
carbon dioxide	0.5	20	0.1
Total	100		867

*) based on the reference environment defined by Szargut *et al.,* (1988)

Efficient use of high quality resources

Figure 4 shows lost work figures for the utilisation of natural gas for various purposes. From this picture it can be concluded that it is the best to use natural gas for those chemical processes in which it eventually ends up in the desired products.

The basic rule behind this conclusion is that the degradation of work-potential has to be delayed as long as possible. This rule facilitates the choice of chemical route and raw materials. For the nitric acid

process, this rule is broken; hardly any fraction of the natural gas adopted as high quality raw material ends up in the nitric acid.

Also, the direct use of high quality natural gas for low quality heating purposes does not coincide with the idea of sustainability.

Towards sustainability

In the discussion about how we should set up our chemical process industry in the (near) future, the sustainability issue is of prime importance. Sustainability in the ecological sense means that we do not place an intolerable load on the ecosphere and that we maintain the natural basis for

The theoretical work-potential of natural gas

A typical composition of Dutch natural gas is given in Table 2, which also presents its pure chemical work-potential. The average delivery pressure of Dutch natural gas is about 60 bara, representing a (physical) work-potential in addition, which is calculated as follows assuming ideal gas behaviour:

$$Ex_{fysical} = R\,T_0 \cdot \ln\left[\frac{P}{P_0}\right] \quad \text{kJ/mol}$$

Since the natural gas is a mixture, the work-potential of mixing should be subtracted from the work-potential of the gas. Assuming ideal gas behaviour, this mixture-term is given by:

$$Ex_{mix} = R\,T_0 \cdot \Sigma \quad [y_i \ln y_i] = 0.95 \text{ kJ/mol}$$

The total theoretic work-potential thus becomes 876 kJ mol^{-1}. Conversion to normal cubic meters then gives a work-potential of 39.1 MJ Nm^{-3} (1 kmol gas = 22.4 Nm^3). The ratio between the theoretical work-potential (Ex) of natural gas and its lower heating value (LHV) is thus 1.0455.

Lost work analysis of hydrogen production based on steam reforming of natural gas

Because the processes described in this paper are not simulated (rigorously), the accuracy with which the lost work analyses have been carried out is submissive to the quality of data available in public literature. Especially for processes involving intermediate products, *e.g.* the production of nitric acid from natural gas via ammonia, data from various sources have been merged making the analysis more complex than the hydrogen-case presented in this box. Nevertheless, the values indicated in Table 1 in the main text are fairly indicative. Here, we present the lost work analysis of a hydrogen production process. Table 3 gives the data applied, which are taken from Giacobbe *et al.* (1992). Hydrogen is produced by conventional steam reforming of natural gas; purification of the hydrogen product is done by pressure swing adsorption. Table 4 presents the results of the lost work analysis. From these results, the thermodynamic efficiency of hydrogen production is 10.53/18.26 = 0.58.

The work-potential equivalent of export steam

Export heat is given in the public literature in many ways. To convert the export steam— which is given in mass by Giacobbe *et al.*—to theoretical work-potential, it is assumed that saturated water at 60 bar ($T_{sat} = 275\ °C$) is evaporated and superheated to 500 °C by process heat, thereby recovering work-potential. On the basis of the thermodynamic relation $Ex_{fys} = \Delta H - T_0 \cdot \Delta S$ and using data from the steam tables, this change of state results in an uptake of 1.06 MJ of work-potential per kg of steam.

Table 3 Minimum amount of input data required for the lost-work analysis of hydrogen production

input					
compression power	0.02	kWh	=	0.072	MJ
natural gas* consumption	4141	kCal	=	17.33	MJ
water	1.78	kg			
output					
export steam	1.2	kg			
hydrogen	1	Nm^3			

*) natural gas is used both as feedstock and as energy source

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Table 4 Lost work analysis of hydrogen production by steam reforming of natural gas*

input				
natural gas	17.33×1.0455	=	18.12	MJ_{ex} / Nm^3 of hydrogen
water			negl.	
air			negl.	
power	$0.072 / \eta_{ex}$ (=50%)	=	0.144	MJ_{ex} / Nm^3 of hydrogen
	Total	=	18.26	
output				
hydrogen	236 kJ/mole	=	10.53	MJ_{ex} / Nm^3 of hydrogen
steam-credit	1.2×1.06	=	1.27	MJ_{ex} / Nm^3 of hydrogen
	Total	=	11.80	
lost work			6.46	MJ_{ex} / Nm^3 of hydrogen
			145	kJ/mole
			72.4	GJ/ton

*) for electricity/power production, an exergetic efficiency of 50% has been assumed (cogeneration process)

life. The complexity of the chemical industry with its numerous products made that we have lost sight of the associated ecological impact of these products' life-cycles: when you produce something, you also produce long-term effects.

Improvement of thermodynamic efficiency is frequently but erroneously considered as the contribution to sustainability. An increase of thermodynamic efficiency, however, has to do with a lowering of the rate with which our non-renewable natural resources are consumed, whereas sustainability implies utilisation of renewable resources such as biomass or solar energy.

Although the figures presented in this paper are quite indicative, they do not reflect the degree of sustainability of the processes but rather their efficiency. In other words, the degree to which they use renewable materials is not given explicitly. Actually, a chemical conversion process can be 100% efficient when all non-renewable work-potential (exergy) ends up in the desired product(s). In real processes, exergy is lost. Hence, more exergy enters the process than leaves it. This excess of exergy entering the process to make it proceed has to originate from renewable sources, such as solar exergy, in order to contribute to sustainability.

Such a 'balanced' process industry can still lead to exhaustion of our natural resources if the exergy-content of the non-renewable end-products is not utilized at the end of the product-life.

If we go one step further, our starting materials should be renewable, *e.g.* carbon dioxide and water. Real sustainable systems/chains need to be circular with respect to matter (outputs become inputs). The driving force for such a sustainable system must stem from solar energy, which is essentially available in large quantity (Figure 5). Wall (1977) and Gong and Wall (1997) give elaborate discussions on exergy and sustainability.

Looking into this matter more carefully, we have come to the insight that the extent to which a process contributes to sustainability can be characterised by three parameters. The first parameter is the one we have discussed before, the thermodynamic efficiency of the process. The second parameter needs to reflect the extent to which use has been made of renewable
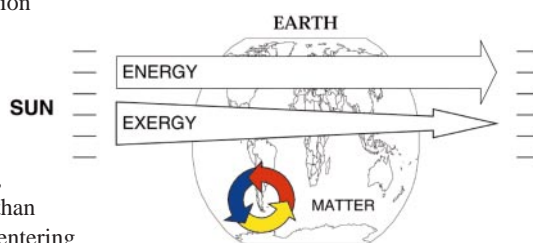
Figure 5 Flows of energy, exergy, and matter on earth (free from Wall, 1977)

resources. Finally, a third parameter is needed to indicate the extent to which circles have been closed. For more details we refer to Van Den Berg *et al*. (1999).

Chemical routes

The work-potential of chemical components can be calculated from thermodynamics. This work-potential can be considered as the minimum work needed to synthesize the specific component from constituents of its surrounding. It has been shown that in practice the production of desired chemicals requires far more work than indicated by the work-potential of this desired product. In other words, the work-potential entering and leaving such processes do not balance, so work is lost. The challenge of our process industry is to limit the losses, while still being able to let our processes run with sufficient speed.

In past decades, increasing energy-efficiency was accomplished mainly by complex heat-integration within existing chemical processes requiring considerable investments.

The lost-work analyses described by Hinderink *et al.* (1996c), however, shows that the chemical reaction step largely determines the overall thermodynamic efficiency. Chemical reactions have been found by us to be a notorious source of lost work. If chemical processes are developed from scratch by state-of-the-art methods—*i.e.* by structured process synthesis procedures—attention can be paid to the core of the process, *i.e.,* the chemical reactions or the chemical reactor. Then, a significant improvement of energy efficiency and process economics can be achieved simultaneously (Harmsen *et al.,* 1999).

Losses resulting from chemical reactions can be viewed similarly to losses resulting from heat exchange. The driving force for heat transfer is the temperature gradient, which not only determines the rate of transfer, but also the degree of devaluation of work-potential. Chemical reactions do also proceed along a gradient from high to low chemical affinity. On flowing along this gradient, heat is released and work-potential is lost. The relation between the Gibbs free energy of reaction and lost work is linear. This relationship has been established by Denbigh (1956) and was discussed by Hinderink *et al.* (1996b). This insight is of prime importance for the development of future chemical routes.

For more sustainable chemical routes, chemical gradients should be reduced, or should be counterbalanced by chemical reactions proceeding against their gradient. In this view, there is an analogy between heat-pinch and reaction-pinch.

FEATURE

Examples of reactions proceeding with a large gradient are the production of nitric acid by the partial oxidation of ammonia and the conversion of H_2S into elemental sulphur and steam. The development of new chemical processes should thus focus on exergy-neutral reactions. In addition, one should also look for sophisticated utilisation of the Gibbs energy of reaction (Harmsen and Hinderink, 1999), *e.g.* by using it directly to drive a separation, *i.e.* reactive distillation. Of course, all future chemistry will still be submitted to the laws of nature.

Renewable resources

Although Figure 3 is fairly indicative, the graph lacks information on which part of the primary work-potential is renewable. If, for example, the energy needed for the metallurgical processes comes from hydro-energy, our conclusions with respect to the improvement-potential of these processes will have to be adapted.

Conclusions

Some general observations from lost work analyses are:

- The extent of lost-work differs from product to product and from process to process and depends largely on how skilled we are.
- Processes showing a large steam credit, although useful, should be distrusted, because this implicitly means that more primary work-potential is applied than actually needed.
- All second law improvements basically have to come from postponing as long as possible the devaluation of work-potential; keep the quality of energy and matter high.

In view of sustainability:

- The best source for work-potential (exergy) is a renewable resource
- A more complete thermodynamic analysis of processes does not only deal with the efficiency but also with the extent to which renewable resources have been used and to which extent ecological cycles have been closed.
- An intuitive approach towards efficiency and sustainability is in our view unacceptable given the importance and urgency of these issues. Therefore, it is advisable to benefit from the quantitative power of the extended thermodynamic analysis proposed.

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Mr. A.P. Hinderink is currently a process engineer/consultant with Process Design Center B.V. where he is involved in many industrial process synthesis projects. He holds a Bachelor of Chemical Technology degree and a Master of Technological Design degree from the Delft University of Technology. The foundation of this paper was laid in 1994, when he worked with the group of professor De Swaan Arons.

After a career of nearly 20 years in the industry, **Jakob de Swaan Arons** became a full professor at the Delft University of Technology. His specific interests are phase equilibria at high pressures and in the critical region, and the efficiency and sustainability of industrial processes.

Hedzer van der Kooi has worked for more than 30 years in the Applied Thermodynamics and Phase Equilibria group within the Department of Chemistry at the Delft University of Technology. After several studies on phase equilibria, for example for natural gas processing, urea production and reversed micelles, he worked for about 10 years on process improvement and recently also on the definition and realisation of sustainability.

Metal-free oxidations

Three groups have recently independently published results on immobilised versions of TEMPO, which are effective in the oxidation of organic substrates.

A group led by Hermann van Bekkum has developed a method for the anchoring of TEMPO via reaction of 4-allyloxyTEMPO with trichlorosilane, followed by grafting of the trichlorosilane onto MCM-41 (M. J. Verhoef, J. A. Peters and H. van Bekkum, (*Stud. Surf. Sci. Catal.,* 1999, **125,** 465). The catalyst was then tested in the oxidation of an α-methyl glucoside:
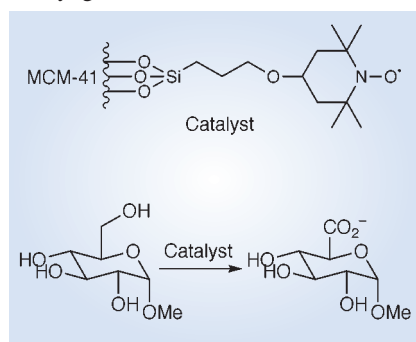
The best results were obtained with sodium hypochlorite. At pH 9, the usual conditions with this oxidant, significant destruction of the base-labile MCM-41 framework was observed, and it was necessary to reduce the pH to 8. Lowering the temperature to 0 °C was also required to control the poorer selectivity of the reagent at this pH. Under these conditions, no leaching occurred. In the same paper the authors also report the oxidation of benzyl alcohol to benzaldehyde with excellent selectivity using the same TEMPO catalyst with an oxygen / CuCl / immobilised TEMPO system.

Meanwhile Carsten Bolm and Thomas Fey (*Chem. Commun.,* 1999, 1795) reported the synthesis of a similar material from aminopropylsilica and the 4-keto derivative of TEMPO, via a reductive amination sequence. This was shown to be an efficient catalyst for the oxidation of primary alcohols to aldehydes, and a reasonably effective oxidant of secondary alcohols. The primary oxidant used was sodium hypochlorite and potassium bromide. Reuse of the catalyst was also demonstrated, with little change in activity over 10 reuses.
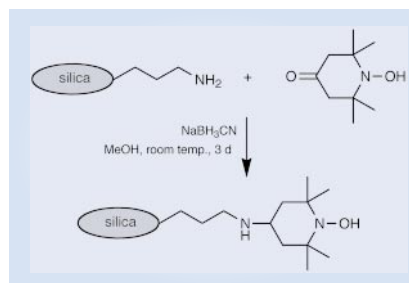
In a related publication (*Stud. Surf. Sci. Catal.* 1999, **125**, 237) Daniel Brunel's group have demonstrated the use of peptide coupling techniques to prepare anchored TEMPO, again via amino-propyl-derivatised Micelle Templated Silica (MTS). Thus, they showed that stably bound amides can be produced using dicyclohexyl carbodiimide or *N*-hydroxy succinimide derivatives of carboxyTEMPO.
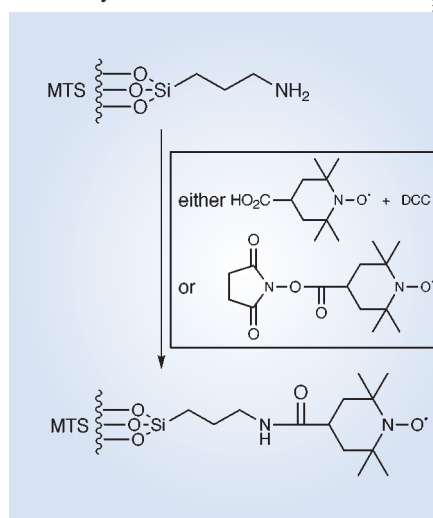
They also provided an elegant method to determine whether the TEMPO units are genuinely bound to the surface. This involves the use of tetrafluoro-TCNQ as an electron acceptor. Chemically bound TEMPO units give charge transfer bands on interaction with the TCNQ derivative. However, physically adsorbed or free TEMPO moieties do not give these charge transfer bands. Thus the colour of the solid after treatment with the TCNQ is a direct and simple indication of the nature of the attachment of the TEMPO units. Such a test will help determine the effectiveness of the coupling at the surface in such catalysts.

Charge Transfer
R = CONH ⁓ SiO₂

no Charge Transfer
R = CO₂H
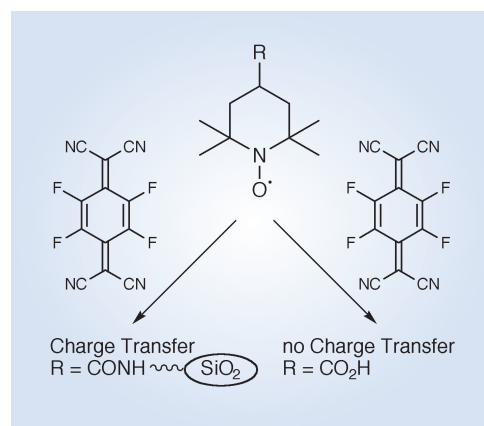
MCM-41 as catalyst support

MCM-41 has also been used as a support for two other interesting new catalysts for oxidation.

A group led by Steven Ley and Brian Johnson has demonstrated the utility of an immobilised form of ammonium perruthenate (*Chem. Commun.,* 1999, 1907). They immobilised the catalyst by protonation of the aminopropyl-MCM41 material with HBF₄, followed by exchange of the anion with potassium perruthenate. The catalyst obtained is very active for the conversion of several benzylic and allylic alcohols, giving quantitative yields of aldehyde or ketone in short reaction times using air as oxidant. Other catalysts derived from trialkylamines and bromopropyl-MCM-41 followed by ion exchange were also tested and found to be equally effective.

X = NH₃⁺, NH₃⁺ RuO₄⁻, Br, NMe₃⁺ RuO₄⁻, NEt₃⁺ RuO₄⁻
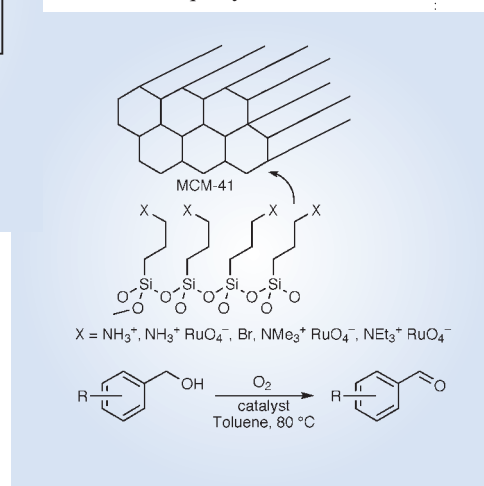
Chi-Ming Che and co-workers have described their work on the asymmetric epoxidation of alkenes using a supported binaphthyl-Schiffs base complex of Cr, which they have immobilised on aminopropyl-MCM-41 (*Chem. Commun.* 1999, 1789).
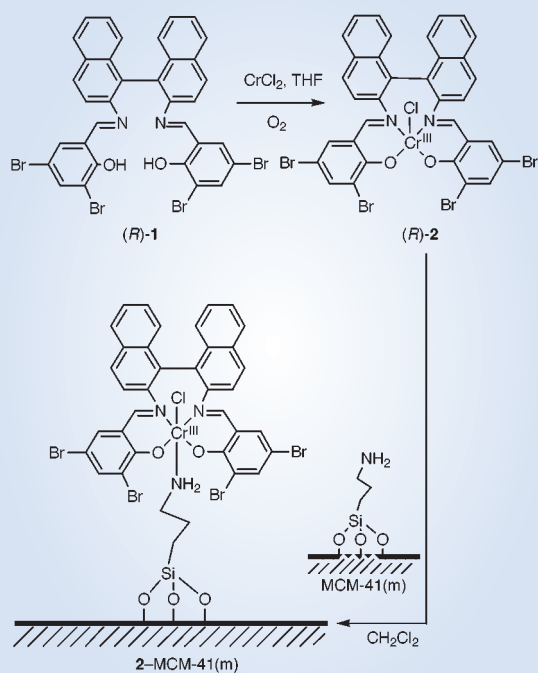
Immobilisation of the Cr complex was achieved under mild conditions, and the complex was used to carry out the epoxidation of a range of alkenes using PhIO as oxidant. Whereas many immobilised chiral complexes lead to lower enantioselectivities than their homogeneous counterparts, in this case ee's were substantially higher (*e.g.* for 4-chlorostyrene the immobilised catalyst gave 65% ee, while the homogeneous equivalent gave only 48%). The recycling of the catalyst was partially successful, with two uses giving identical results, the third slightly poorer, and the fourth substantially worse. Total turnover numbers were over 200 with good ee, then an additional 77 turnovers could be achieved at lower ee. The increase in ee is unusual and interesting, especially in light of the opportunities for control of the pore size and surface chemistry which is possible with such supports.

Hydroformylation of alkenes

The hydroformylation of alkenes continues to be a fertile area for catalyst innovation. The Ruhrchemie-Rhône-Poulenc process (based on a water-soluble phosphine-Rh complex) is an excellent example of this (see, for example, *CHEMTECH*, 1987, 570). However, it is limited to low molecular weight alkenes. Peter Wasserscheid and co-workers from the RWTH-Aachen have

developed a novel methodology based on ionic liquids to get round this problem (*J. Catal.*, 1999, **186,** 481). They studied the hydroformylation of methyl 3-pentenoate, a potential new intermediate for the production of adipinic acid and nylons. They found that excellent reactivity and selectivity could be obtained in the ionic liquid reaction media. Furthermore, the lack of volatility of the ionic liquid, coupled with its good thermal stability, meant that the products could be distilled out of the reaction system, leaving the catalyst dissolved in the ionic liquid. This solution could be reused directly in a second reaction. Further reaction cycles led to a slow deactivation. However, using conventional solvents, the catalyst is left in the distillation residues (if it is not extracted first, a difficult and inefficient step) and can no longer be used after the first cycle. These initial results indicate that the catalyst lifetime can be readily increased by the use of ionic liquids, without a change in selectivity. Such an innovation improves both the environmental impact of the process and its economics.

Hydrogenation of ketones

The enantioselective heterogeneous hydrogenation of ketones has been studied by several groups over the last decade or so. The most promising system
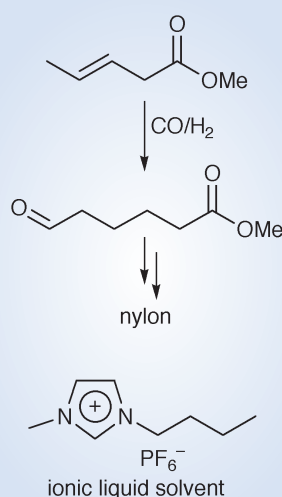
involves the use of Pt/alumina modified with naturally occuring alkaloids such as cinchonidine. These systems can deliver excellent enantioselective excesses in the hydrogenation of a range of ketones to alcohols. Alfons Baiker and his group have now demonstrated that a continuous hydrogenation of activated ketones such as ketopantolactone and ethyl pyruvate is possible if the chiral modifier chinchonidine is fed continuously into the reactor at ppm levels. (*J. Catal.,* 1999, **126,** 239) Interestingly, the addition rate required for optimum ee was dependent on the type of reactor used, but other operating parameters had less influence. The enantioselectivity achieved was 83.4% for the lactone and 89.9% for the less reactive ethyl pyruvate.
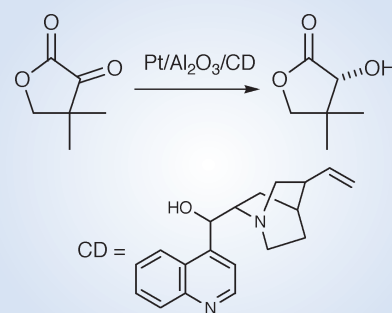
Energy-efficient microwave synthesis

French scientists at the IUT Département Chimie, Besançon, have been comparing the effects of microwave irradiation and classical heating on the intramolecular cyclisation of 2-hydroxyphenylacetic acid (*J. Chem. Soc., Perkin Trans. 2*, 1999, 2111). By using an optical fluorescence technique, Jean Marie Mélot and colleagues were able to make accurate measurements of local temperatures in the reactor (Figure 1). Although they found no intrinsic difference in reaction rates using the two different heating methods, they did conclude that the transfer of energy to the reaction was much more efficient under microwave conditions: the whole reaction process required just 108 kJ using microwaves, whereas the classically heated reaction consumed over 3500 kJ.

Hydroxylamine oxidations using bleach

Nitrones are useful building blocks in organic synthesis, but are commonly pro-
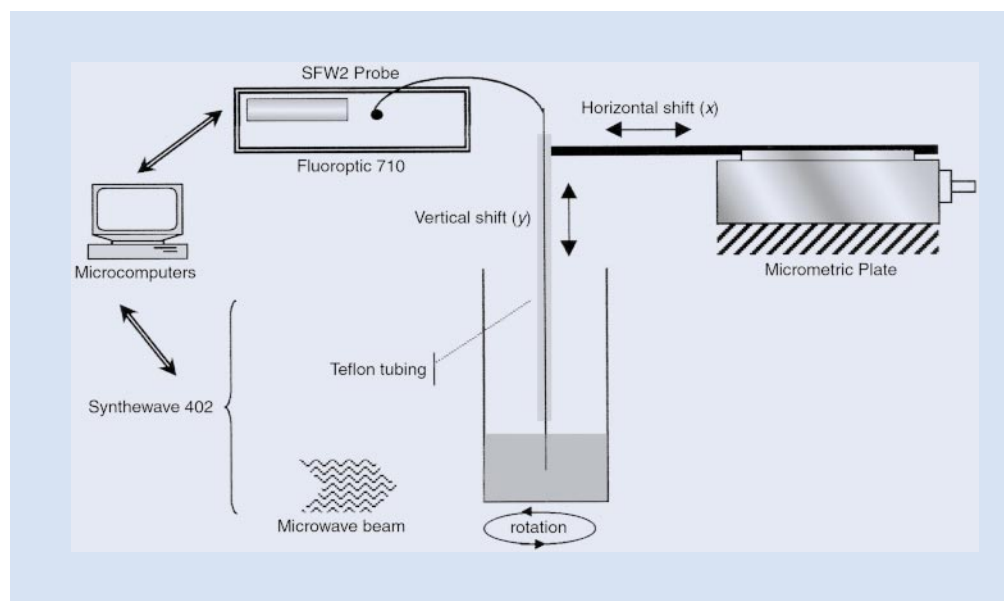
**Figure 1** *Measurement of local temperatures by optical fluorescence*

duced by oxidation of hydroxylamines using highly toxic mercury salts, or other heavy metal reagents. Research conducted by Andrea Goti and co-workers at the Universitá degli Studi di Firenze in Italy has led to a new method for hydroxylamine oxidation which is much more environmentally acceptable (*J. Org. Chem.*, 1999, **64**, 7243). A wide range of substituted nitrones were prepared in high yield (50–92%) by reaction of hydroxylamines with aqueous sodium hypochlorite solution at room temperature, with the yields and selectivities being comparable to those obtained using HgO. Household bleach was found to be just as effective for this transformation as commercially supplied 13% sodium hypochlorite.
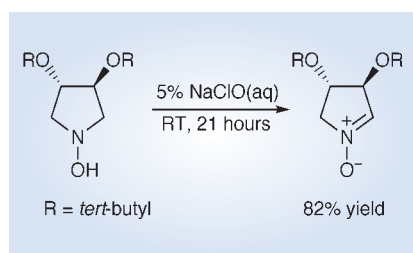
Direct synthesis of iodoalkanes

Dr Peter Schreiner and colleagues at the Institut für Organische Chemie der Universität, Göttingen, Germany, have discovered a simple and efficient method for the direct iodination of unactivated hydrocarbons (*Angew. Chem., Int. Ed.*, 1999, **38**, 2786). Unlike other free-radical halogenation reactions, iodinations are markedly endothermic, which prevents a

chain reaction occurring, and so iodoalkanes had to be prepared by reaction of an alcohol or another haloaromatic. The new reaction involves simply stirring the unfunctionalised alkane with sodium hydroxide and iodoform at room temperature, either without a solvent if the alkane is liquid, or in dichloro-methane for heavier solid substrates. Yields vary considerably, but are in the 70–95% region for several substrates.
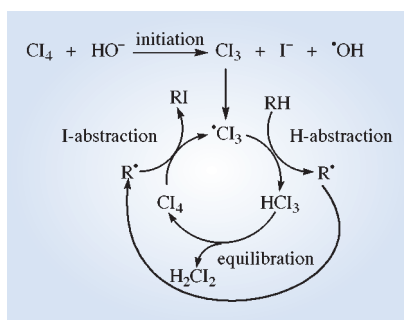
Polyurethanes

Since polyurethanes were first produced 60 years ago they have been prepared by mixing two chemical components, and the plastics are actually formed in the moulds of the upholstery or shoe-sole manufacturers etc. Now, chemists E. W. Meijer, Ron M. Versteegan and Rint P. Sijbesma, at the University of Eindhoven (*Angew. Chem., Int. Ed.* 1999, **38**, 2349–2354), have now found a way to include both polyurethane components in one and the same molecule; these building blocks can be used to easily construct types of polyurethane that could only be

synthesised in a roundabout way before.

The basic building blocks of polyurethanes are molecules that contain alcohol and isocyanate groups. In principle these groups act as 'button' and 'buttonhole'; the building blocks, which each have either two buttons or two buttonholes, automatically link together in a reactor to form long chains.

Clearly, it would be easier to include both 'button' and 'buttonhole' in the same molecule, so only a single type of building block would be produced.

This already works in the synthesis of the related polyamides (Nylon, Perlon), which are constructed in a similar fashion—only starting from acids and amines. Until now, complicated tricks had to be used to get this to work for polyurethanes, because the crucial isocyanates could only be synthesised under conditions that are unfriendly to the alcohols, causing them to undergo other reactions. This is where the team from Eindhoven comes in—they found a chemical that builds up isocyanates in a very gentle way, under conditions that leave any alcohol groups in the molecule untouched. In this way, Meijer and his coworkers could actually produce polyurethanes that contain only one type of building block.

The physical characteristics of these [n]polyurethanes are very promising. Whether they will be accepted in industry, however, mainly depends on whether the simple building blocks can easily be produced in large quantities.

Diols

At the Institute of Organic Catalysis Research in Rostock, Matthias Beller, Christian Dobler and Gerard Mehltretter have been able to produce diols (used as antifreeze, as basic building blocks for a variety of plastics, and in the synthesis of many pharmaceuticals) in a single step from oxygen and olefins (*e.g.* ethylene or propylene) using osmium compounds as catalysts (*Angew. Chem., Int. Ed.* 1999, **38**, 3026–3028).

Currently diols are synthesised in two steps. Indeed it has been known for some time that diols could be synthesised from

PERSPECTIVES

olefins in one step when osmium compounds are used as a catalyst. Industry has not been able to make use of these one-step processes, however, because they required large quantities of expensive oxygen-containing specialty chemicals, whose synthesis generated large quantities of waste. The new Rostock process. By using oxygen gas, is both highly economical and more environmentally friendly.

Beller's team is not the first to experiment with oxygen and osmium; earlier attempts, carried out by other chemists decades ago, under aggressive conditions, led to the destruction of the newly-formed diols by the metal and the idea was abandoned.

Catalyst for air purification

A room temperature catalyst for efficiently converting carbon monoxide into carbon dioxide has been developed by Graham Hutchings and Stuart Taylor of Cardiff University working with Ali Mirzaei at the Leverhulme Centre for Innovative Catalyst at the University of Liverpool (*Chem. Commun*., 1999, 1373). The catalyst, the first room-temperature catalyst based on copper zinc oxide for oxidising carbon monoxide, could be used in more effective and cheaper-to-run air purifiers at industrial sites, in mining and for deep sea and space exploration to avoid carbon monoxide poisoning. The catalyst is far more effective than the commonly used hopcalite (mixed manganese copper oxide) catalyst, although its structure must now be optimised. The team prepared their catalyst using co-precipitation under different gases—air, nitrogen, hydrogen and carbon dioxide. Each preparation effectively mixes copper(II) oxide and zinc oxide to form a highly dispersed mineral containing a 'solid solution phase'. Composition depends on preparation gas, the ageing between preparation and filtering the solid from the liquid. The catalysts were tested for carbon monoxide oxidation power at 20 °C under a steady flow of carbon monoxide. All the copper zinc oxides were highly active, but the most active were those prepared in air and aged for one hour. The team is now studying the mechanism of oxidation more closely with a view to optimising the preparation conditions.

Ionic liquids continue to impress

Ionic liquids are currently attracting considerable attention as green solvents. The properties of ionic liquids that make them potentially green include their ability to dissolve many different chemicals, including rock and coal, and the fact that they are non-volatile, inflammable and are non-toxic. Professor Claude de Bellefon and his team at the Laboratoire de Génie des Procédés Catalytiques in France have recently discovered other properties of ionic liquids that may lead to greener chemical processes in the near future. The team compared ionic liquids with water as catalyst support media in 'liquid–liquid' biphasic catalysis (*J. Mol. Catal. A: Chemical*, 1999, **145**, 121). They studied the palladium catalysed Trost-Tsuji C–C coupling reaction (see Scheme) and apart from the ease of separation of the catalyst (also true of the water system) found the following advantages over the water system.
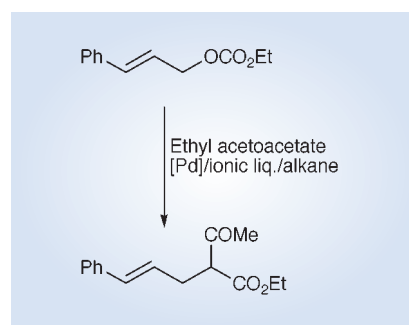
The ionic liquid dissolves the organic reagents to a greater extent than water, which means that a higher substrate/catalyst ratio can be used and the reaction rate is enhanced. Palladium chloride is soluble in the ionic liquid and can therefore be used as the Pd(0) precursor instead of palladium acetate. Formation of cinnamyl alcohol (a side-reaction involving water as a nucleophile) is suppressed, and furthermore, simple alkane co-solvents can be used as in place of nitrile solvent required in the aqueous regime. Further work is in hand to use this chemistry in a continuous reactor to evaluate the catalyst deactivation and the product separation.

Read any green chemistry papers?

If you have any items from your literature reading which could be included 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]

Oilseed rape and wheat—two crops where industrial uses are being explored.

Alternative ways of turning green into gold

Industry, agencies and Governments throughout the EU are committing effort and resource to the development of new technologies needed to support major changes in raw material sourcing. The latest conference, GRIF'99, at the John Innes Centre, Norwich, UK, in November—organised by ACTIN, the leading authority in the UK on industrial crops—has recently identified 'drivers for change' in the move towards greater reliance by industry on crop-derived raw materials.

Although more than 80% of the world's energy and raw material needs are currently derived from mineral oil, gas and coal, there are increasing concerns in industry and government over the sustainability of a reliance on fossil resources; particularly, the impact of this on the level of CO_2 in the atmosphere, which is seen as a major contributor to the greenhouse effect.

Farmers already have a small part to play in reaching this target by supplying biomass in the form of farm and crop residues and short rotation coppice for electricity generation. However, plants, which use the sun's energy to convert CO_2 into polysaccharides and other complex molecules, also have tremendous potential to become a renewable source of high quality raw materials for industry.

Delegates at GRIF'99 learnt about new aspects of research in starch metabolism and the underlying genetics in cereals, new polymers and plastics being developed by industry, composite materials for the automotive and building industries and the potential to produce speciality chemicals and high added value products in plants including milder detergents, inks, dyestuffs and agrochemicals.

Of particular note was ICI's biodegradable product *Eco-Foam*, made from modified maize starch. This has the same soft resilient features as polystyrene but, unlike the conventional product, it dissolves in the presence of water. *Eco-Foam*, or the Novamont (Italy) product *Mater-Bi* which has complementary properties, could replace huge tonnages of long-lived plastic packaging made from fossil fuels and destined for landfill.

Earlier this year, the aptly named 'Oilseed Rape Pipeline' seminar was the first *crop-based* seminar held by ACTIN (Alternative Crops Technology Interaction Network). Oilseed rape is probably the most developed of the industrial, *i.e.* non-food, crops in the UK and, accordingly, there were diverse papers ranging from Warwick University to Mobil Oil Company. The seminar attracted 70 delegates from a wide variety of backgrounds who debated the rapidly improving scientific understanding of possible genetic, chemical and physical modifications to the crop and its current and potential uses as a renewable raw material for industry.

Oilseed rape is now the third most important crop in the UK after barley and wheat with nearly 500,000 hectares under cultivation. Globally, it is ranked as the third most important oilseed crop after soybean and palm.

University research in the UK on the crop's metabolism is world class and on par with the US. Current research programmes, funded by Home-Grown Cereals Authority (HGCA), into physico-chemical modifications are highlighting the versatility of the crop and the potential importance of rapeseed oil as a feedstock for polymers and oilseed rape meal in biocomposite manufacture.

Croda, an industrial user of high erucic rape oil (HERO) for erucamide production, described the extensive collaboration which took place over a period of years with British farmers, MAFF and European authorities to re-establish HERO as crop grown in the UK for industrial users.

Rapeseed oil-based polyols have also been successfully introduced in rigid polyurethane systems, currently being used in commercially-acceptable production of moulded parts for the automotive industry, with resultant environmental and financial advantages. Manufacturing plants for rigid foam polyols derived from natural oils are now being sold worldwide, particularly to Eastern Europe and the Asia Pacific regions. There is also the prospect of high functionality foams 100%-derived from rapeseed oil feedstocks.

Oilseed rape based oils have developed a niche position in the UK lubricants market but despite having some intrinsic advantages in their environmental impact, they have not fulfilled their potential, partly due to a lack of legislation.

The economic and environmental viability of the pipeline is being addressed through detailed 'whole systems' approaches, *e.g.* Lifecycle
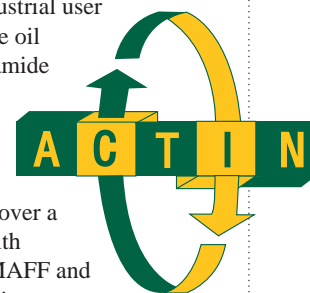
(LCA) and Cost Benefit Assessment (CBA) studies.

Agenda 2000, the most recent reform of the EU's Common Agricultural Policy, is effectively removing the oilseed premium from the farming industry. However, this should not have a significant effect on the supply of oilseeds within the UK/EU as the crop will have an important long term role in balanced arable rotations. Alternatively, any perceived long-term supply insecurity could be overcome with stable, fixed-price supply contracts.

In conclusion, the seminar noted that manufacturers can be confident of:

● a secure supply of raw material
● at a competitive 'crude oil' price
● which can satisfy market expectations
● for a number, perhaps an increasing number, of non-food applications

Baroness Hogg, who is Chairman of a House of Lords Science and Technology Sub-Committee inquiring into non-food crops, which will be reporting in December, recently wrote (*Financial Mail* on Sunday, 5 September 1999): 'Today, or at least tomorrow, we will be able to grow all kinds of valuable compounds that at present we manufacture synthetically. These range from vaccines to packaging materials. There is great environmental advantage to be gleaned from such natural production, from the use of biodegradable rather than synthetic materials. These have to be balanced against the use of genetic techniques that might be needed to make some of these products viable. There are no magic solutions here to the troubles of the agricultural sector, to reform of CAP, to environmental policy or to the needs of the rural economy. But there is potential for the enterprise culture to play its part in the resolution of these difficulties.'

Industry is also recognising the importance of sustainability in the 21st Century and the enormous variety of opportunities arising from renewable feedstocks. Dr. Robert R. Dorsch, director of biotechnology development at DuPont, has stated, 'Essentially all of society in the last 100 years has been built on petroleum as the energy and raw material. We need to go from black gold to green gold'.

For its own part, ACTIN has planned a strategic calendar of relevant events for 2000, including 'Industrial Uses of Wheat' (Cambridge, 22 March 2000) with speakers including DuPont and Hunstman Polyurethanes.

The Oilseed Rape Pipeline and GRIF proceedings are available from the ACTIN Help Desk, Tel +44 (0)1372 802054, E-mail info@actin.co.uk, www.actin.co.uk; as are further details of ACTIN itself - a 'not for profit' organisation - their 2000 calendar and a 'Report of Activities 1997-1999'

Nigel Oliver, ACTIN,
15 November 1999.

York Green Chemistry Symposium

The Green Chemistry Network held a one-day symposium at the end of September 1999 in York. The symposium, which was kindly sponsored by Zeneca Agrochemicals, brought together younger workers in the field from local universities to discuss their work. One of the main aims of the symposium was to demonstrate the interdisciplinary nature of green chemistry and to encourage a 'team' approach to solving real issues. Topics covered during the symposium included heterogeneous catalysis, process intensification, supercritical fluids and ionic liquids. Full details of all the speakers and abstracts of the presentations can be found on the GCN web site http:/www.chemsoc.org/gcn.

Karen Wilson, who has been working with James Clark for several years and has recently been appointed as a lecturer at York started the day with a paper on 'New Solid Acids For Organic Synthesis'. The talk centred around the use of mesoporous silica functionalised with Lewis [BF_3, $AlCl_3$, $Zn(OTf)_2$] and Bronsted acids (RSO_3H) for carrying

out industrially important organic transformations. Specific examples included alkylation, etherification and isomerisation of aromatics. These reactions are often carried out by acids which are not recovered at the end of the reaction and are major contributors to waste streams generated by the fine chemicals industry.

Helen Theyers, a Ph.D. Student from Hull working with Adam Lee, continued the heterogeneous catalysis theme. Heterogeneously catalysed oxidation reactions for fine chemicals synthesis is advantageous because this can avoid the production of environmentally unacceptable waste produced by traditional stoichiometric methods, facilitate use of simple clean oxidants, *e.g.* air and H_2O_2, and simplify product separation.

The selective oxidation of cinnamaldehyde and cinnamaldehyde over carbon supported PGM catalysts and the effect of promoter, support, solvent and temperature were discussed. Cinnamaldehyde oxidation proved difficult giving poor yields. Greater selectivity was obtained using pre-reduced catalysts, and surprisingly unpromoted catalysts were more selective. Selectivity decreased with temperature as combustion commenced.
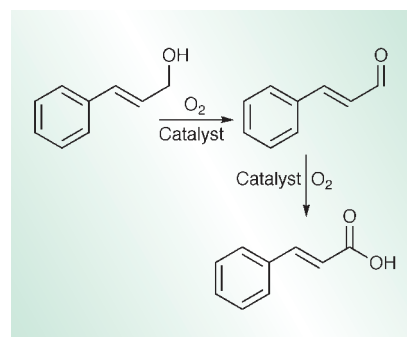
Speakers at the York Green Chemistry Symposium, left to right: Karen Wilson (University of York), Matthew Giles (University of Nottingham), Helen Theyers (University of Hull), Keith Gray (Nottingham), Kamelia Boodhoo (University of Newcastle), Rajiv Bhalla (University of York), Nicola Meehan (University of Nottingham).

Cinnamyl alcohol oxidation to cinnamaldehyde resulted in much higher conversions (18%) with 98% selectivity. For both reactions carbon supported catalysts appear more selective than graphite counterparts.

Chemical engineering has a huge role to play in green chemistry; the most Eco-friendly processes of the future will undoubtedly be developed by chemists and engineers working together. Kamelia Boodhoo, a post-doctoral fellow in the Process Intensification & Innovation Centre at Newcastle University gave a talk on spinning disc reactors (SDR) and how they can be used to both drastically reduce the size (and cost) of processing equipment and improve process efficiency. SDR's are a potentially attractive choice of reactor for systems which are or become heat or mass transfer limited, *e.g.* polymerisation reactions or inherently fast reactions. Possible applications in polyester and polystyrene manufacture were discussed; advantages of the SDR in these applications include lower energy use and production of more controlled narrower molecular weight distribution.

Advantages and applications of super-critical fluid technology were explored in three presentations from Nottingham University. Nicola Meehan gave an over-view of supercritical fluid technology; making the highly valid point that even though use of $scCO_2$ offers many environmental advantages as a benign replacement for more toxic solvent, due to the cost of high pressure equipment, it is only likely find applica-tions where there are technical as well as environmental benefits. Nicola's pre-sentation centred on development of supercritical hydrogenation technology in conjunction with Thomas Swan. This technology opens up the possibility of having small 'on demand' hydrogenation reactors of interest to fine chemicals man-ufacturers. The same technology is also showing promise for dehydrogena-tion reactions.

Matthew Giles presented a paper on stabilisers for polymerisation in super-critical carbon dioxide, an area which has received much attention since DeSimone's *Science* paper in 1992. Dispersion polymerisation of acrylates in $scCO_2$ suffer from production of low molecular weight material due to polymer insolubility. By adding stabilisers, which have a $scCO_2$ soluble group such as siloxane or fluorocarbon as well as an acrylate soluble moiety, the polymer can be stabilised until much

higher molecular weights have been built up. By varying the length of siloxane chain for example some control over polymer morphology, molecular weight and yield can be exerted.

More efficient and Eco-friendly ways of carrying out Friedel–Crafts reactions was a recurring theme during the day. Keith Gray highlighted the contribution supercritical technology is able to make in this area. In the reaction of phenol with an alkylating agent the reaction can be tuned to give preferential C or O alkylation. Using similar technology the Nottingham group have also investigated the synthesis of cyclic ethers; in particular an improved method for the synthesis of THF from 1,4-butanediol has been studied.

Dr Rajiv Bhalla, Postdoctoral fellow working with Paul Dyson at York gave a presentation covering hydrogenation reactions using novel biphasic approaches. The design and synthesis of a variety of chiral phosphine ligands was described and there use with Ru and Rh based catalysts in ionic liquid–organic and ionic liquid–water biphasic systems for carrying out a variety of organic trans-formations discussed. Ionic liquids clearly increase the activity of catalysts of this type and offer high potential for highly selective waste-free processes.

The keynote presentation was given by Professor Ken Seddon of Queen's University, Belfast. Ken is well-known as a leading expert in the field of ionic liquids and gave an extremely interesting overview of the potential applications and environmental benefits ionic liquid based processes may offer. The potential number of ionic liquids available is truly enormous and current research has hardly scratched the surface, by tailoring the components the property of the liquid can be varied widely. The environmental benefits largely result from the avoidance of volatile organic solvents; ionic liquids however also offer many technical advantages including:

● large liquid range (*ca*. 300 °C).
● thermal stability
● Bronsted, Lewis and Franklin acidity
● excellent solvent properties

Potential industrial applications of ionic liquids include alkylation, acylation, polymerisation and catalysis of Diels–Alder reactions.

Also at the meeting the RSC Process Technology Group presented their Award for Clean and Efficient Processing to BP Amoco for the CATIVA acetic acid process. Accepting the award Dr Derek Watson described how this new methanol

carbonylation technology using, an iridium catalyst, reduced the E-Factor by some 30% through improving energy efficiency and reducing liquid waste by-products (propionic acid). Carbon dioxide emissions have been reduced from 0.48 te / te acid to 0.318 te / te acid. It world production of acetic acid were converted to CATIVA the saving would be 270,000 tpa CO_2 compared to the Monsanto process. Apart from environ-mental benefits there is also a saving of some 30% on the cost of new plant.

Mike Lancaster

Corporate Environmental Leadership Seminar

The ninth annual Corporate Environmental Leadership Seminar will be held June 4–15, 2000 at Yale University in New Haven, Connecticut. As the leading executive program of its kind, the Corporate Environmental Leadership Seminar offers a comprehen-sive curriculum emphasizing Emerging Issues and Environmental Leadership Development. The 2000 Seminar features many new sessions designed to provide essential information and sharpen decision-making tools for the difficult tasks facing senior environmental managers. Case studies, discussions, and exercises highlight the cross-disciplinary aspects of environmental problem solving, in view of conflicting scientific analyses and changing conditions.

The curriculum is divided into three clusters:
● Science for Environmental Management and Policy
● Law, Economics & International Environmental Management
● Environmental Leadership in a Time of Change

A small class size encourages exchange among a diverse group of participants representing government agencies, non-governmental organizations and a broad range of private business.

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DIARY

Conference Diary

January 2000
2nd Asia-Pacific Congress on Catalysis January 31
Sydney, Australia –February 2
(http://www.chemsoc.org/events/_events/
00001018.htm)

February 2000
AAAS Annual Meeting and Science February 17–22
Innovation Exposition including a workshop
on Sustainability through Science
Washington DC, USA
(http://www.aaas.org/meetings/2000/index.htm)

Hazard Analysis in Chemical Industry February 27
(HACI) and Inherently Safer –March 1
Plant Design (ISD)
Kanpur, India
(jpg@iitk.ac.in)

March 2000
Process Design and Operation for March 5–9
Sustainable Development
The Hilton Hotel, Atlanta, USA
(http://www.cpe.surrey.ac.uk/staff/aa.htm)

Green Chemistry March 15
University of York, UK
(http://www.chemsoc.org/events/_events/00002021.htm)

Biocatalysis as a tool for organic synthesis March 20–22
Crowne Plaza Hotel, Amsterdam,
The Netherlands
(http://www.scientificupdate.co.uk/pages/biocatalysis/
biocat.html)

Industrial Uses of Wheat March 22
The Chilford Halls,
Cambridge, UK
(info@actin.co.uk)

INBIO Europe 2000: Biocatalysis— March 23–24
New Science and Applications
Crowne Plaza Hotel, Amsterdam,
The Netherlands
(http://www.scientificupdate.co.uk/pages/inbio/inbio.html)

Teaching the Environmental Sciences in March 25
the Millennium
Including a session on Green Chemistry
Scientific Lecture Theatre, Burlington Place,
London, UK
(greennet@york.ac.uk)

ACS National Meeting including Green March 26–31
Chemistry for Reduction of Greenhouse
Gas Emissions
San Francisco, California, USA
(http://www.lanl.gov/greenchemistry/conf.htm)

April 2000
Green-Tech® 2000— April 3–5
Sustainable Raw Materials
Royal Dutch Jaarbeurs, Utrecht, Netherlands
(http://www.europoint-bv.com)

Hazards XV-
The process, its safety, and the April 4–6
environment - getting it right
UMIST, Manchester, UK
(mikeadams@valrichardson.com)

5th International Symposium on April 8–12
Supercritical Fluids: 'Supercritical Fluids
for Sustainable Technology'
Westin Atlanta North Hotel, Atlanta, Georgia, USA
(http://www.issf2000.org)

Wood and Cellulose: Building Blocks April 9–12
for Chemicals, Fuels and Advanced Materials
SUNY-EST, Syracuse, New York, USA
(http://www.epa.gov/opptintr/greenchemistry/calendar.htm)

Rapid Process Development and Safe April 12
Process Scale-Up
North London, UK
(http://www.helgroup.co.uk/index.cfm/page.news)

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

9th International (and 4th European) April 13–14
Symposium on Supercritical Fluid
Chromatography and Extraction.
In cooperation with Analytica Conference 2000
Munich, Germany
(sfc2000@mx.uni-saarland.de)

RSC Annual Conference including April 16–20
Symposium 'Towards Sustainability'
UMIST, Manchester, UK
(http://www.rsc.org/lap/confs/sciprog.htm)

InLCA: The International Conference and April 25–27
Exhibition on Life Cycle Assessment
Cincinnati, USA
(InLCACI@epamail.epa.gov)

May 2000
Synthetic Methodology and May 16
Total Synthesis: New Horizons in Natural
Product Chemistry
University of Glasgow, UK
(http://www.rsc.org/lap/rsccom/dab/perkidiv.htm)

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

Pinacol coupling of aromatic aldehydes and ketones.

An improved method in an aqueous medium

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Summary

Reductive coupling of aromatic aldehydes and ketones leading to 1,2-diols has been achieved with high yield and good diastereoselectivity under environmentally friendly conditions using aluminium powder in the presence of aqueous sodium hydroxide. The notable advantage of the present method seems to be the negligible formation of side products arising mainly due to reduction of the carbonyls to the corresponding alcohols, Cannizzaro reaction and formation of olefins *via* McMurry coupling. Diaryl ketones have been found to be unreactive under the present conditions. Moreover, the aluminium recovered after the reaction can be reused after washing and drying.

Introduction

The pinacol coupling reaction,[1] although discovered way back in 1859,[2a] still finds many applications in the diastereoselective synthesis of vicinal diols which can be used as intermediates for the construction of biologically important natural product skeletons.[2b–d] Numerous reagents for pinacol reactions are known, which include the uses of Al–Hg,[3a] Rieke Mg,[3b] active Mn,[3c] SmI_2,[3d] SmI_2–TMSCl (TMSCl = trimethylsilyl chloride),[3e] Cr(II) complexes,[3f] Sm–Et_2AlI,[3g] Zn–TMSCl–Ti(III),[3h] $TiCl_3$[3i] and titanium–Schiff base complexes,[3j] to name a few. There are also reports of pinacolization in absolute methanol using Al–KOH[4a] and Sm–I_2–Ti(OPr^i)$_4$;[4b] these methods require absolutely anhydrous conditions in an inert atmosphere. Moreover many of these reagents are costly, moisture-sensitive and toxic. It is, therefore, very significant to develop a new methodology for this important C–C bond formation reaction by identifying alternative reaction conditions and by utilization of less toxic reagents and solvents, in order to improve environmental performance. Recently, in connection with environmental concerns, there has been growing interest in using water as a reaction medium.[5] Water offers several advantages with regard to cost, safety, selectivity[5] and operational simplicity compared with the use of organic solvents. $TiCl_3$,[6a] (Cp$_2$TiCl)$_2$-catalyzed[6b] and metal-mediated (Zn–$ZnCl_2$,[7a] Mg,[7b] Mn[7c] and In[7d]) stereoselective pinacol couplings in aqueous media have already been reported. During a study on the reduction of cycloalkanones with Al–Hg in aqueous THF (9:1) to the respective alcohols by Hulce and LaVaute,[8] benzaldehyde, acetophenone and benzophenone were found to undergo coupling reaction, but no detailed and systematic investigation was undertaken. As a part of our endeavour to study metal-mediated reactions in aqueous conditions, we report herein a simple and mild method for pinacol coupling of aromatic aldehydes and aryl methyl ketones by aluminium powder in aqueous basic medium

(Scheme 1). Aluminium is known to be less toxic than some of the reagents[3a,c,f–i] which have already been reported for pinacol coupling.
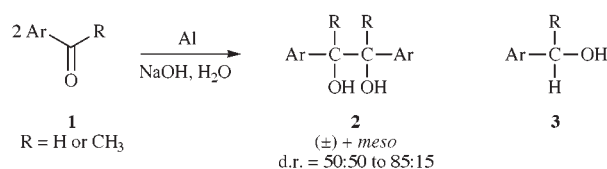
Scheme 1

Results and discussion

In a typical general procedure, to a vigorously stirred suspension of the carbonyl compound in 0.5 M aqueous sodium hydroxide solution was added commercial aluminium powder and stirring was continued at room temperature till the completion of reaction (as monitored by TLC). The results are reported in Table 1. The products were isolated by the usual work-up procedure which is discussed in the Experimental section. The residue after the reaction contained a mixture of unreacted metallic aluminium (to the extent of about 60%) and aluminium hydroxide. The unreacted aluminium can be recycled after washing the residue with 1 M HCl followed with water and drying.

As shown in Table 1, several structurally different aromatic aldehydes underwent reductive coupling to the corresponding 1,2-diols (**2**) in high yields. The reaction rates were faster than those in many existing methods,[3f,7b–d] and the products were

Green Context

This is one of two papers in this issue of *Green Chemistry* which describes the successful use of water as a solvent for the pinacol reaction. The reductive coupling of carbonyl compounds is a powerful method for constructing C–C bonds. There are many known methods for achieving this involving several reagents but many of them suffer from drawbacks such as high cost, toxicity or handling problems. The ideal synthetic method for pinacol reactions would combine high yield, good diastereoselectivity, no side reactions and minimal waste of low toxicity. In this paper a new general synthetic procedure employing aluminium powder in aqueous base is described that brings together these desirable features. *JHC*

Table 1 Aluminium-mediated pinacol coupling in aqueous media

Entry	Ar	R	Reaction time/h	Yield of **2** (%)[a]	Yield of **3** (%)[b]	$(\pm):meso$ in **2**[c,9]
1	C_6H_5	H	2	89	0	50:50
2	$4\text{-}CH_3C_6H_4$	H	3	83	0	51:49
3	$4\text{-}ClC_6H_4$	H	2	80	0	59:41
4	$4\text{-}CH_3OC_6H_4$	H	2	85	0	68:32
5	$2\text{-}CH_3OC_6H_4$	H	2	80	0	70:30[d]
6	$2\text{-}ClC_6H_4$	H	2	62[f]	6	48:52
7	$3,4\text{-}(CH_3)_2OC_6H_3$	H	3	76	0	85:15
8	$4\text{-}C_6H_5CH_2O\text{-}, 3\text{-}CH_3OC_6H_3$	H	4[g]	54[e]	0	80:20[d]
9	C_6H_5	CH_3	3	70	Trace	65:35
10	$4\text{-}CH_3OC_6H_4$	CH_3	6	65[f]	5[f]	72:28
11	$4\text{-}CH_3OC_6H_4$	CH_3	6[g]	Trace	36[f]	—
12	$4\text{-}CH_3C_6H_4$	CH_3	6	50[f]	16[f]	Not determined
13	$4\text{-}ClC_6H_4$	CH_3	6	75[f]	3[f]	76:24
14	C_6H_5	C_6H_5	5	0	0	—
15	C_6H_5	C_6H_5	2[g]	0	95[a,g]	—
16	$4\text{-}CH_3C_6H_4$	C_6H_5	6	0	0	—
17	$4\text{-}CH_3C_6H_4$	C_6H_5	2[g]	Trace	80[a,g]	—
18	$4\text{-}ClC_6H_4$	C_6H_5	6	0	0	—
19	$4\text{-}ClC_6H_4$	C_6H_5	2[g]	0	94[a]	—

[a] Unless otherwise mentioned yield refers to the isolated pure product, fully characterized by ^{1}H NMR spectroscopy. [b] Obtained by ^{1}H NMR (300 MHz). [c] $(\pm):meso$ was measured by ^{1}H NMR (300 MHz) based on the intensities of benzylic protons. [d] Measured by ^{1}H NMR of quantitatively acetylated product(s). [e] For entry 8, 40% of the starting material was recovered. [f] Yield is calculated in terms of % of conversion by ^{1}H NMR (300 MHz). [g] Reactions were carried out using $MeOH:H_2O=2:1$ and excess aluminium (>10 eq) and excess NaOH (>10 eq).

obtained in higher yields and much better purity compared to those from the earlier method using Al–Hg.[3a] Another important aspect of this process is the formation of much smaller amounts of the reduced product (**3**) (e.g. entries 4, 5, 6 and 9), which makes it synthetically more useful.[4b,7a,b] Besides, the competing Cannizzaro reaction, giving alcohol and carboxylic acid, was not observed and there was also no olefin formation arising from McMurry reactions. In general, the vicinal diols were obtained with better[3f,4a,b,7b,c] diastereoselectivity in favour of $(\pm)$-isomers compared to some of the earlier reports.[3f,4a,b,7b,c] Coupling reactions of substituted aryl methyl ketones by the present method have been found to be sensitive to the electronic and steric effects of the substituents. The electron donating (inductive and mesomeric) groups seem to decrease the extent of conversion. Diaryl ketones are reluctant to couple under the present conditions. Diaryl ketones were completely reduced to the corresponding benzhydrols (entries 15, 17, 19) in the presence of excess aluminium (>10 eq) and sodium hydroxide (>10 eq) in a solvent system of $MeOH:H_2O = 2:1$; whereas they were recovered unaffected (entries 14, 16 and 18) when the reaction was carried out in water alone.

In this reaction system water seems to play a major role in enhancing the rate of reaction, probably due to hydrophobic packing[5a] of the ketyl radical anions on the reactive metal surface within the critical distance of C–C bond formation. The coupling of ketyl radical anions seems to take place in an aqueous medium at a much faster rate compared to further electron transfer from the aluminium surface resulting in preferential formation of the diol over the reduced alcohol. This gains support from the fact that in the reactions of benzaldehyde and p-anisaldehyde using the present reagent composition (substrate:Al:NaOH = 1:3:1.5) in absolute methanol (in place of water) the unreacted substrates were isolated almost exclusively, even after stirring for ten hours. Water probably also has some

Table 2 Diastereoselectivity [$(\pm):meso$ ratio] for the products obtained by coupling of p-anisaldehyde using aluminium and alkali in different solvent systems

Entry	Solvent system	$(\pm):meso$[9]
1	H_2O	68:32
2	$Acetone:H_2O = 1:2$	69:31
3	$THF:H_2O = 1:2$	71:29
4	$1,4\text{-}Dioxane:H_2O = 1:2$	63:37
5	$Bu^tOH:H_2O = 1:2$	75:25
6	$MeOH:H_2O = 1:2$	79:21
7	MeOH	52:48[4a]

Yields of isolated pure products are above 80% and the extents of formation of the reduced product are negligibly small in all cases.

stereodirecting effect towards the coupling procedure as is evident from Table 2.

Improved diastereoselectivity has been observed in aqueous media in a number of cases (in water alone as well as using different water-miscible cosolvents) compared to the analogous process by Khurana et al.[4a] in absolute methanol using substrate:Al:alkali = 1:2:6.

Conclusions

The present aluminium-mediated procedure in aqueous media provides a very useful, economically viable and environmentally friendly pinacol coupling of aromatic aldehydes and aryl methyl ketones. The important advantages offered by this procedure include (a) operational simplicity, (b) high yield and purity of coupled products, (c) low cost and (d) improved diastereoselectivity. Aluminium is known to be a relatively less toxic material

compared to many of the reagents used for pinacol coupling and the unreacted aluminium can be recycled after proper treatment. Reduction of waste can be achieved by reuse of resource. Therefore this approach to pinacol coupling has set out to minimise the dispersion of offensive materials in the environment and maximise the use of renewable resources. For these reasons it can be considered as relatively green technology. Further investigations on the mechanistic and stereochemical aspects of this method and its application to organic synthesis are currently underway.

Experimental

General procedure for aluminium-mediated pinacol coupling in an aqueous medium

In a typical general procedure, to a vigorously stirred suspension of freshly distilled benzaldehyde (530 mg, 5 mmol) in aqueous sodium hydroxide (15 ml, 0.5 M) was added commercial aluminium powder (405 mg, 15 mmol). Stirring was continued at room temperature till completion of the reaction (as monitored by TLC). The reaction mixture was then filtered and the residue was washed with water (2 × 5 ml) followed by ethyl acetate (4 × 10 ml). The aqueous filtrate was diluted with water (20 ml) and repeatedly extracted with ethyl acetate (3 × 20 ml). The organic extracts and washings were combined, washed with water (2 × 10 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure to leave the product as a white solid, which was further purified by crystallisation using dichloromethane and light petroleum (b.p 40-60°C) to leave hydrobenzoin (478 mg, 89%) as white flakes, as a mixture of diastereomers; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.36–7.10 (10H, m), 4.82 (s) for O–C–H of *meso*, 4.69 (s) for O–C–H of (±)[9] (total 2H), 2.91 (br, OH), 2.27 (br, OH).

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Optimization of pinacol coupling in aqueous media

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Summary

The optimization of magnesium as well as Al–KOH mediated pinacol coupling of benzaldehyde is described. Exchange of the magnesium turnings for magnesium powder permitted the use of a significantly lower excess of magnesium and shortened the reaction time, while the conversion of starting material as well as the yields of products were preserved. Ultrasound had a beneficial effect on the reaction using magnesium. Using water instead of methanol as the reaction medium for Al–KOH mediated reactions resulted in raising the yields. The lowering of the Al:KOH ratio was also possible.

Introduction

Carbon–carbon bond formation is one of the most important topics in organic synthesis. One method for carbon–carbon bond formation is pinacol coupling. Many modifications of this reaction have been described in recent reviews.[1–3] In most of the described methods anhydrous conditions and long reaction times are necessary to achieve high yields of the products. On the other hand, Zhang and Li[4,5] descibed a simple and effective method for pinacol coupling reactions of various aromatic aldehydes and ketones in acidic aqueous media mediated by magnesium. The yields of pinacols were 40–90%, but the reaction time necessary to achieve such good yields was 12–24 h and molar ratios of Ar–CHO:Mg turnings as high as 1:20 were necessary.

Another promising method for pinacol coupling mediated by aluminium–KOH was described by Khurana and Sehgal.[6] This method is very rapid (5–10 min) and the yields of pinacols are 87–98%. The reaction medium was methanol and a molar ratio of Ar–CHO:Al:KOH = 1:2:6 was used in this reaction.

The main goal of this work was to make an attempt on the optimization of the last two methods.[5,6] The emphasis was to lower the aldehyde:Mg ratio in the first method and to replace methanol with water as the reaction medium in the second method.

Results and discussion

In our previous paper we examined the ultrasound effect on the pinacol coupling reaction under the conditions described by Zhang and Li,[4,5] and found that ultrasound considerably accelerates the benzaldehyde conversion (Scheme 1).
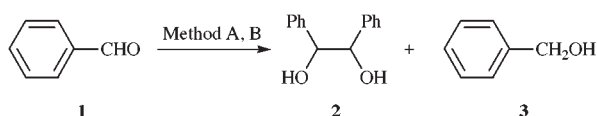
Scheme 1 Method A: Mg turnings or powder; 0.1 M NH$_4$Cl or H$_2$O; silent or)))). Method B: Al–KOH; CH$_3$OH or H$_2$O; silent reaction.

The control, silent experiments revealed that the reaction times given in Zhang's papers[4,5] were overestimated. At the beginning of this work we decided therefore to study the reaction time effect on the course of this reaction. From the results given in Table 1 it follows that complete conversion of benzaldehyde was achieved in 90 min in sonochemical experiments, while 180 min was necessary to obtain the same conversion in silent experiments. Similar reaction time effects were also observed for the pinacol coupling of 4-chlorobenzaldehyde under the same conditions.

The benzaldehyde:Mg molar ratio of 1:20 is very bad from the atom economy point of view and we decided therefore to investigate whether this ratio is necessary and to examine the effect of Mg quality on the course of the reaction. From the results given in Table 2 (entries 2–4) it follows that, when using magnesium turnings, changing the Ph–CHO:Mg ratio to 1:10 lowers the conversion of the starting material to 67.7% and further lowering this ratio to 1:5 caused a decrease in the conversion to 35%. The same results were achieved using recovered Mg turnings (entries 5 and 6) and fresh Mg turnings in both silent and sonochemical experiments.

On the other hand, when magnesium powder was used instead of magnesium turnings it was possible to shorten the reaction time to 10 min (Table 2). The most important discovery was that decreasing the benzaldehyde:magnesium (powder) ratio to 1:10 had no influence on conversion of the starting material. Further lowering of the molar ratio of benzaldehyde to magnesium to 1:1 caused a reduction in the conversion of the silent reaction to only 50% (Table 2).

Lowering the molar excess of magnesium turnings in the sonochemical experiments to 1:5 and 1:2 had no significant effect on the conversion of benzaldehyde (Table 2, entries 10, 12). Sonication of the reaction mixture with a 1:1 molar ratio raised the conversion to 58%, but a more pronounced ultrasound effect was observed in experiments with a 2:1 molar ratio. The silent experiments gave just 6% conversion of benzaldehyde, while the sonochemical experiments gave a benzaldehyde conversion of 43.7% (Table 2, entries 15 and 16).

Green Context

Like the paper by Bhar and Panja, this paper describes a new synthetic procedure for the pinacol reaction that is based on water as the reaction solvent. Water offers many practical and economic advantages as a reaction solvent, including low cost, safe handling and environmental compatibilily. This article shows how two different metal reagents can both be successfully used in the pinacol coupling of benzaldehyde in water.   *JHC*

Table 1 Dependence of magnesium mediated pinacol coupling of benzaldehyde on reaction time

Run	Reaction conditions	Time/min	Conversion of **1** (%)	**2** (%)	Proportion of (±):*meso* of **2**	**3** (%)
1	))))	15	75.3	91.7	1:1	8.3
2	))))	30	84.3	93.3	4:5	6.7
3	))))	60	92.6	93.3	4:5	6.7
4	))))	90	100	95.0	4:5	5.0
5	silent	90	69.7	88.3	1:1	11.7
6	silent	180	92.5	99.1	4:5	7.5

Molar ratio of **1**:Mg (turnings) was 1:20.

Table 2 Influence of quality and quantity of magnesium on pinacol coupling of benzaldehyde

Run	Mg	Molar ratio **1**:Mg	Reaction conditions	Time/min	Conversion of **1** (%)	**2** (%)	Proportion of (±):meso of **2**	**3** (%)
1	turnings	1:20	silent	90	69.7	88.3	1:1	11.7
2	turnings	1:20	))))	90	100	95.0	4:5	5.0
3	turnings	1:10	))))	90	67.7	92.9	1:1	7.1
4	turnings	1:5	))))	90	34.9	82.2	3:4	17.8
5	turnings[a]	1:20	silent	90	65.2	85.2	1:1	14.8
6	turnings[a]	1:20	))))	90	92.2	93.4	3:4	6.6
7	powder	1:20	silent	10	98.3	97.3	1:1	2.7
8	powder	1:10	silent	10	96.8	82.8	1:1	17.2
9	powder	1:5	silent	10	69.8	84.6	1:1	15.4
10	powder	1:5	))))	10	97.9	87.4	1:1	12.6
11	powder	1:2	silent	10	60.1	81.7	3:4	18.3
12	powder	1:2	))))	10	90.0	85.1	1:1	14.9
13	powder	1:1	silent	10	50.4	80.2	3:4	19.8
14	powder	1:1	))))	10	58.6	86.7	3:4	13.3
15	powder	2:1	silent	10	5.9	80.2	1:1	19.8
16	powder	2:1	))))	10	43.7	100	1:1	0

[a] Recovered magnesium.

We attempted to improve the benzaldehyde conversion at Ph–CHO:Mg (powder) ratios of 1:1 or 2:1 by prolonging the reaction time to 20 min. To our surprise the conversion of benzaldehyde conversion and the pinacol yield of both silent and sonochemical reactions mediated by magnesium powder were the same as after 10 min reaction. We do not have any explanation for these peculiar results.

From the green chemistry point of view it is of interest to determine whether addition of NH$_4$Cl to the water medium is necessary. The results in Table 3 show that pinacol coupling of benzaldehyde mediated by magnesium could be carried out equally well in pure water and in 0.1 M NH$_4$Cl. This method has synthetic utility (Table 3, entries 5 and 6) since only a slight lowering of the conversion was observed when the reaction was performed with tenfold amounts of reactants in both 0.1 M NH$_4$Cl and pure water.

The second target of this work was to improve pinacol coupling mediated by Al–KOH. To start this study, we decided to make a preliminary survey of the pinacol coupling reaction and compare our results to those of Khurana. We were not able to achieve as high yields in methanol as Khurana described (87–93%).[6] This is probably a consequence of different qualities of aluminium powder. From the green chemistry point of view it would be of interest to change the reaction medium and to lower the Al : KOH ratio. As can be seen in Table 4, the conversion of benzaldehyde is substantially higher in pure water than in methanol. Conversion of the starting material after 10 min in methanol was 46.1%, while in water it was 98.3%. Lowering the

molar excess of KOH resulted in lowering of the conversion. The conversion of benzaldehyde in methanol decreased from 46.1% to 11.0% and in water from 98.3% to 56.4% when the molar excess of KOH was reduced fourfold. The reactions performed in pure water gave a conversion of benzaldehyde after 20 min of more than 90%, despite the lowering of the molar excess of KOH (Table 4, entries 9 and 12).

The pinacol coupling mediated by Al–KOH and the method mentioned above have synthetic utility. A tenfold increase in the amount of reactants caused only a slight lowering of the conversion (Table 4, entries 4, 5 and 6).

Conclusions

1. The reaction time described by Zhang and Li[4,5] for silent pinacol coupling mediated by magnesium was overestimated.
2. Using magnesium powder instead of magnesium turnings allows the reaction time to be reduced and the molar excess of magnesium, to be lowered.
3. The conversion of benzaldehyde in the reactions mediated by Al–KOH was higher in pure water than in methanol.
4. It is possible to decrease the molar excess of KOH in Al–KOH mediated pinacol coupling in water.
5. Both methods metioned above have synthetical utility.

Experimental

All chemical reagents were commercially available. The aluminium and magnesium powders (both more than 10 years old) were obtained from Lachema (Czech Republic), the magnesium

Table 3 Influence of reaction medium and reaction conditions on magnesium mediated pinacol coupling of benzaldehyde

Run	Reaction medium	Reaction conditions	Time/min	Conversion of 1 (%)	2 (%)	Proportion of (±):*meso* of 2	3 (%)
1	0.1 M NH$_4$Cl	silent	90	69.7	88.3	1:1	11.7
2	water	silent	90	58.1	84.7	1:1	15.3
3	0.1 M NH$_4$Cl	))))	90	100	95.0	4:5	5.0
4	water	))))	90	94.5	87.2	3:4	12.8
5	0.1 M NH$_4$Cl [a]	))))	120	90.7	80.1	3:4	19.9
6	water [a]	))))	120	92.5	78.0	1:1	22.0

Molar ratio **1**:Mg (turnings) was 1:20. [a] Reaction performed with 40 mmol of benzaldehyde.

Table 4 Influence of reaction medium and quantity of KOH on pinacol coupling of benzaldehyde

Run	Reaction medium	Molar ratio of 1:KOH	Time/min	Conversion of 1	2 (%)	Proportion of (±):*meso* of 2	3 (%)
1	methanol	1:6	5	15.4	94.8	1:1	5.2
2	methanol	1:6	10	46.1	96.6	4:5	3.4
3	water	1:6	5	65.2	92.2	1:1	7.8
4	water[a]	1:6	10	98.3	91.8	4:5	8.2
5	water[b]	1:6	10	79.5	86.5	1:1	13.5
6	water[b]	1:6	20	94.1	84.6	4:5	15.4
7	methanol	1:3	10	12.2	94.7	1:1	5.3
8	water	1:3	10	61.6	91.9	1:1	8.1
9	water	1:3	20	96.0	96.2	1:1	3.8
10	methanol	2:3	10	11.0	88.3	5:3	11.7
11	water	2:3	10	56.4	92.4	5:3	7.6
12	water	2:3	20	93.0	91.3	4:5	8.7

[a] Reaction performed with 5 mmol of benzaldehyde. [b] Reaction performed with 50 mmol of benzaldehyde.

turnings were obtained from Aldrich. Benzaldehyde (Lachema) was distilled before application in pinacol coupling reactions.

The ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in CDCl$_3$ with TMS as an internal standard. Conversion of starting material, (±):*meso* ratio and pinacol:alcohol ratio, respectively were measured by ^{1}H NMR spectroscopy based on the intensities of the benzylic protons signals.

General procedure for pinacol coupling mediated by magnesium

A suspension of benzaldehyde (446 µl; 4 mmol) and magnesium turnings (2 g; 83 mmol) in 0.1 M NH$_4$Cl (20 ml) was stirred at room temperature under an air atmosphere. The reaction was quenched with 3 M HCl (20 ml) and the organic compunds were extracted with ethyl acetate (3 × 50 ml).The combined organic layers were washed with saturated aqueous KHCO$_3$ solution and brine, dried over anhydrous Na$_2$SO$_4$ and filtered. Ethyl acetate was evaporated *in vacuo* and the crude product was analyzed by ^{1}H NMR spectroscopy.

Sonochemical reactions were irradiated in a thermostated glass reactor fitted to an ultrasonic horn UUA 001 Ultragen (20 kHz, 300 W) under pulsed conditions (pulse length: 4 s; 50%) at room temperature under an air atmosphere. The reaction mixture was then processed as described above.

General procedure for pinacol coupling mediated by Al–KOH

A suspension of benzaldehyde (500 µl; 5 mmol), aluminium powder (0.269 g; 10 mmol) and KOH (1.68 g; 30 mmol) in methanol (10 ml) was stirred for 10 min at room temperature under an air atmosphere. The reaction mixture was filtered to remove the aluminium powder and water was added to the

filtrate. The organic compounds were extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. Ethyl acetate was then removed by a vacuum rotary evaporator. The crude products were analyzed by ^{1}H NMR spectroscopy.

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Hydrolysis of soybean oil

in a subcritical water flow reactor

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Summary

Subcritical water has been recently demonstrated to be a viable medium for conducting hydrolysis reactions on a variety of organic compounds. In this study, the hydrolysis of triglycerides in soybean oil to their respective free fatty acids has been affected using a flow reactor. The flow reactor permits hydrolysis to be accomplished without the need of a catalyst but requires higher temperatures than previously used in a static system to attain >97% product conversion. Using a high pressure view cell as a diagnostic aid, it was found that the oil miscibility with water is crucial to attaining a high conversion to the free fatty acids. Water to oil ratios of 2.5:1–5:1 were found to optimal for high conversions as well as residence time between 10–15 minutes in the open tubular reactor. Such rapid hydrolysis times contrast with multi-hour conversions utilized industrially to achieve a 96–98% fatty acid yield. Although conversion of the all natural *cis* forms of the fatty acids to some *trans* form occurred, the isolated products were clear and free of degradation products, unlike previous results reported for the reaction run in a closed vessel under static conditions at these elevated temperatures (>300 °C). Determination of the *trans* fatty acid content of aqueous hydrolyzed oils has not been previously reported, however they are of minor importance since the produced fatty acid mixtures are primarily intended for industrial utilization and not for food consumption.

Introduction

The exploration of new reaction media and conditions to yield environmentally-benign manufacturing processes offers new challenges and opportunities under the name of 'green chemistry'[1]. Reviews of such 'green' options have been summarized by several authors[2,3] and the synthetic possibilities using critical fluid media by others.[4–6] Such fluids avoid many of the problems associated with organic solvents, including flammability, product contamination, and the costs associated with solvent disposal. To date, many of these critical fluid processes have utilized supercritical carbon dioxide (SC-CO$_2$), due to its low cost, attractive critical constants, and relative inertness.[7,8]

Water, in its supercritical region (SC-H$_2$O), and its subcritical analogue, have also receiving increasing interest as an alternative to using organic solvents.[9] The critical properties of SC-H$_2$O are higher (T_c = 374 °C, P_c = 24.2 MPa and ρ_c-=-0.32 g mL^{-1}), relative to those for SC-CO$_2$. Water has the capability of dissolving a variety of organic solutes, since its dielectric constant (permittivity) can be adjusted as a function of temperature while under external pressure. Under appropriate conditions, pressurized water can solubilize even the most nonpolar, hydrophobic organic compounds.[10,11] This property of sub- and SC-H$_2$O has

been exploited since the early 1980s for the destruction of hazardous waste,[12] and more recently for selective and controlled degradative synthesis of organic compounds.[13–15] Recently, Clifford and co-workers have demonstrated the potential of subcritical water as an extraction agent, and shown it to be competitive with steam distillation for the processing of natural products.[16,17]

Specific synthetic organic reactions have been conducted using water in its near-critical or critical state. The oxidation of alkyl aromatics,[18] metal-catalyzed organic transformations,[19] acylation of phenols,[20] as well as the dehydration of alcohols[21] are but a few examples of synthetic possibilities. Recently, Aleman *et al.*[22] have utilized subcritical water for the hydrolysis and saponification of benzoate esters.

Hydrolysis reactions have also been important for many years in the oleochemical industry. Name processes/reactions, such as the Twitchell process,[23] or Colgate-Emery synthesis[24] of complex mixtures of fatty acids have historically been conducted at low pressures and elevated temperatures; although the Eisenlohr[25] process utilized pressures up to 24.2 MPa. It is interesting to note that processes like the Colgate-Emery synthesis are conducted at subcritical conditions with respect to the physical state of water (250 °C and 5.0 MPa), although historically they have not been interpreted as such because the oil to water ratio is usually 2:1, suggesting more of a steam-based hydrolysis, than a subcritical process. The above processes are generically referred to as 'fat

Green Context

Fatty acids form an important group of products, which are used in a range of applications. Their production from sustainable resources is thus a worthwhile venture, with triglycerides being an obvious source. The hydrolysis of these natural products, without the use of acids or alkalis, which lead to salt streams upon neutralisation, is a particularly attractive route. This paper describes the use of sub-critical water as an efficient reagent and reaction medium for the preparation of fatty acids. (See also *Green Chemistry*, 1999, 1, 65 for other work with sub-critical water). One of the key variables in high pressure water is the increased miscibility of organics, even hydrophobic materials such as oils. This miscibility is shown to be very important for a rapid and complete hydrolysis. While some isomerisation of the double bond is seen in unsaturated fatty acids, the route described represents an attractive new route with minimal waste generation. *DJM*

splitting' and a patent application[26] cites the use of subcritical water for affecting this reaction, although the given examples, degree of hydrolytic efficiency, and reaction conditions in this patent would not necessarily be attractive to industry.

Previously we have demonstrated that hydrolysis of vegetable oils can be rapidly achieved in a closed reactor without the need for a catalyst.[27] In this study we have extended the concept using a flow reaction system similar to that used in conventional fat splitting. Hydrolysis is conducted in an open tube without internal mixing elements or catalytic agents, at volumetric proportions where the water content in the reactor exceeds that of the vegetable oil. Reaction conditions have been studied at temperatures between 250–340 °C in the above reactor and in a sight glass to visually observe the process.

Results and discussion

Residence time (flow rate), temperature, pressure and the water to oil ratio were all studied to find the conditions where the hydrolysis yields would be optimal with limited degradation of the oils. Consequently, the majority of the reactions were run with a residence time between 7 and 15 minutes and in the temperature range of 270–340 °C.

Table 1 illustrates some of the conditions that were determined to be appropriate for quantitative conversion of the oil to the free

Table 1 Comparison of results for the subcritical water flow reactor system

Residence time/min	14.8	12.6	9.9	7.8	14.8
T/°C	338	338	338	338	330
P/MPa	13.1	13.1	13.1	13.6	13.1
Water : Oil	5 : 1	2.5 : 1	5 : 1	2.5 : 1	5 : 1
Free fatty acid (%)[a]	99	98	100	90.4	99
Monoglyceride				6.1	
Diglyceride				1.7	
Triglyceride				trace	

[a] Normalized percent free fatty acid based on GC analysis.

fatty acids. The hydrolysis of soybean oil; whose fatty acid composition was: palmitic (12.6%), stearic (4.6%), oleic (26.0%), linoleic (51.0%), and linolenic (5.8%), readily occurred between 10 to 15 minutes of residence time at 330–340 °C in the flow system. Optimal results were obtained at water to oil ratios between 2.5 : 1 and 5 : 1. Lower water/oil ratios produced incomplete hydrolysis, while higher ratios produced no improved conversion. Under the above conditions, reaction times shorter than ten minutes resulted in reduced yields of the free fatty acids, but in all cases, hydrolysis was completed in 15 minutes. Analysis of the incomplete reaction product mixtures by supercritical fluid chromatography indicated the presence of intermediate hydrolysis products, such as mono- and di-glycerides, as well as trace amounts of the starting triglycerides, as indicated by hydrolysis with the shortest residence time (7.8 min) in Table 1.

In all of the experiments, the collected water phase was milky white in appearance, consisting of an emulsion containing the free fatty acids. Initial experiments utilized temperatures starting at 270 °C, based on previous studies on the hydrolysis of triglycerides in a static, batch reactor system.[27] However, in contrast to the previous study, reactions at 270 °C, using the flow reactor and a residence time of 30 minutes, yielded only 22% conversion to free fatty acids.

To try and answer the disparity between the two studies (static *vs.* flow hydrolysis methods), the reaction chamber was replaced with the a high pressure view cell. This arrangement, shown in

Fig. 1, permitted observation of the oil and water phases under hydrolysis conditions. The conditions of the flow view cell were
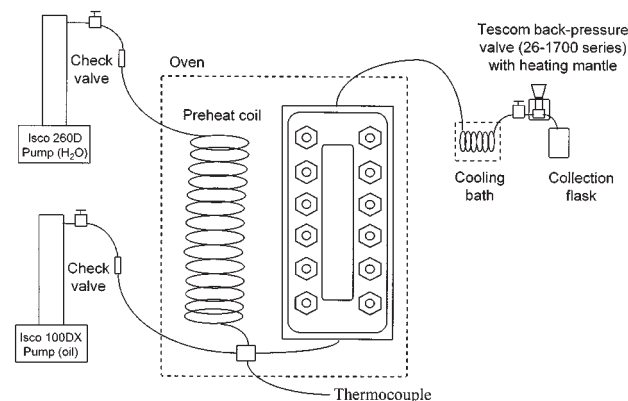
Fig. 1 Schematic of a view cell for subcritical water vegetable oil hydrolysis flow studies.

set such that the water/oil would have a residence time of 14 minutes and sufficient back pressure to keep the water from boiling (12.1–15.2 MPa). When hydrolysis was performed at 300 °C, a mixture was obtained consisting of 34% free fatty acids and significant amounts of mono- and di-glyceride. Under these conditions, it was observed that the soybean oil moved slowly up the window as a sphere, in which, a white solid initially formed, and then the solid slowly dissolved as it travelled on through the cell. Although flow conditions were set to assure an oil residence time of 14 minutes, the residence time in the cell of the oil was less than 2 minutes. This was due to the fact that it was not completely soluble with water at 300 °C, and the oil being less dense than the water, quickly gravitated to the top of the cell, thereby not allowing complete hydrolysis to be achieved.

When the water temperature was increased to 325 °C, the free fatty acid yield increased to 56%, although the water and oil had not become totally miscible. Then as the temperature of the water was slowly increased towards 340 °C, the reaction was closely watched, and at 339 °C, the oil droplets totally disappeared, indicating complete miscibility of the oil and water. At this temperature, the hydrolysis of the oil was complete indicating that for fast and complete hydrolysis, the oil needs to become totally miscible with the water.

Gas chromatographic fatty acid methyl ester (GC-FAME) analysis was also performed on all samples to determine if any degradation or isomerization occurred to the constituent fatty acids during hydrolysis. The major saturated acids, palmitic and stearic, were stable and unaffected under the above described conditions. The principle unsaturated fatty acids in soybean oil, oleic and linoleic, and linolenic acid did not degrade but did undergo some isomerization from the *cis* (*c*) to the *trans* (*t*) isomer. Migration of double bonds was also further verified by the formation of conjugated linoleic acid.

Table 2 lists the fatty acid isomers produced in the hydrolysis reaction as well as the minimum and maximum percentage for each in the completed reactions (> 97% hydrolysis). The variation in the observed conversion of *cis* to *trans* isomers proved to be dependent on the time and temperature that the hydrolysis was conducted under. The minimum conversions were observed at lower temperatures or short residence times, while the maximum conversion was attained at higher temperatures or longer reaction times. This isomerization of the free fatty acids, also occurred for incomplete hydrolysis conducted between 270 to 320 °C, although not to as great an extent as seen at 330 to 340 °C. The *c, t, t* and *t, c, t* as well as the *c, t, c*

Table 2 Isomerization of soybean oil in flow system

Isomer	Minimum (%)[a]	Maximum (%)[a]
t 9-Oleic	1.9	6.1
t 11-Oleic	0.7	3.2
t,t Linoleic	1.0	5.0
c,t Linoleic	2.2	10.3
t,c Linoleic	1.9	10.1
c,t,t & *t,c,t* Linolenic	Trace	0.9
t,t,c Linolenic	Trace	1.1
c,t,c & *c,c,t* Linolenic	Trace	0.5
t,c,c Linolenic	Trace	0.8
conjugated Linoleic	0.7	2.6

[a] Normalized percent free fatty acid based on GC analysis.

and *c, c, t* linolenic acids could not be separated under the reported GC conditions and are reported as a sum for the above isomers. These isomer distribution patterns were found to be consistent during the course of the hydrolysis studies. Gas chromatographic analysis of the starting soybean oil contained none of the *trans*-containing acids reported in Table 2, which indicates that formation of *trans* fatty acids is entirely due to the hydrolysis process.

Since in traditional oleochemical synthetic methods, application of high pressure tends to decrease isomerization, several reactions were performed at higher pressures to tests its effect on the resultant products. The use of higher pressures (up to 40.4 MPa) showed no appreciable reduction in the isomerization of the fatty acids, as can be seen in Table 3. In fact the results in Table 3 indicate a small decrease in the amount of *c,c*-linoleic acid that is present as pressure is increased.

Table 3 Effect of increased pressure on isomerization

P/MPa	16.2	20.2	30.5	40.4
T/°C	330	330	330	330
% *c,c* Linoleic[a]	35.0	32.2	31.9	30.4

[a] The initial soybean oil contained 50% *c,c* linoleic acid. Normalized percent free fatty acid based on GC analysis.

Conclusions

The use of a subcritical water flow reactor has proven to be an effective means of hydrolyzing soybean oil to free fatty acids. Hydrolysis occurs rapidly, within 10 to 15 minutes at temperatures between 330 and 340 °C yielding 97% or better conversion; without the needed for catalysts, emulsifying agents, or any reactor internals. These conversion times and corresponding yields are improvements over those currently used in the fat splitting industry, and are partially achieved by using a high water : oil ratio to suppress glycerol formation in the aqueous phase which inhibits fatty oil hydrolysis. Hydrolysis under these conditions does produce some isomerized fatty acids from the all natural *cis* (*c*) form to *trans* (*t*) isomer, data heretofore unreported, and which unfortunately do not exist for fatty acids produced under conventional industrial hydrolysis procedures. The quoted hydrolysis conditions differ from those previously determined to be optimal for a batch reaction, suggesting caution in extrapolating batch reactor conditions into flow reactor systems.

Experimental

The soybean oil [refined, bleached, deodorized (RBD)] used in these studies was obtained from Archer Daniels Midland, Granite

City, IL. Deionized water was used without further purification. The high pressure flow reaction system, Fig. 2, consisted of an
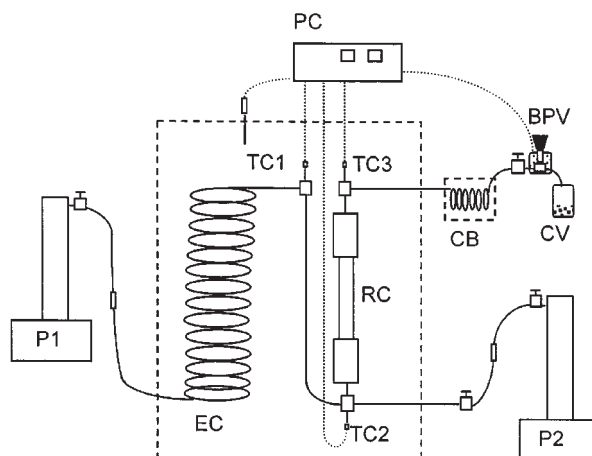
Fig. 2 Schematic of subcritical water flow reaction system in an oven. P1 and P2 are pumps, TC1–3 are thermocouples, EC is a equilibration coil, PC is process controller, RC is the reaction chamber, CB is a cooling bath, BPV is a back pressure regulating valve, and CV is the collection vial.

Isco 260D syringe pump (Isco, Inc., Lincoln, NE) for the water which then entered an oven (Model 3710A, ATS, Inc., Butler, PA) in 1/8" o.d. by 0.30" i.d. Hastelloy-C tubing. The preheated water from the coil went through a tee and then to a cross (all fittings and tubing from High Pressure Equipment, Erie, PA), both of which were equipped with a thermocouple (Type K, 1/16" inconel sheath, Omega Engineering, Stanford, CT). At the cross, the soybean oil was introduced to the system from a Isco 100DX syringe pump. The water–oil mixture then passed through the reaction chamber which consisted of a Hastelloy-C, 8" long, coned and threaded tube (1" o.d., 9/16" i.d., internal volume of 35.5 mL and a pressure rating of 138 MPa), fitted with 1" to 1/8" unions at both ends. The water/oil mixture continued to another tee fitted with a thermocouple, then out to the reservoir of a cooling bath (Model 801, PolyScience, Inc., Niles, IL), through a back pressure relief valve (Model 26-1722, Tescom Corp., Elk River, MN), and finally into a beaker for collection. The first thermocouple was connected to a controller (Part No. CN4800, Omega Engineering, Stanford, CT) which regulated the oven temperature, while the other thermocouples were connected to a digital meter to obtain an accurate reading of the water temperature, both before and after the reaction chamber.

Supercritical fluid chromatographic (SFC) analysis of the reaction products was performed on a Dionex Model 600 SFC (Dionex Corporation, Sunnyvale, CA). The SFC unit was equipped with a timed injector (200 nL injection loop) which was held open for 0.5 seconds; and a Dionex SB-Phenyl-50 capillary column (10 m × 50 μm i.d., 0.25 μm film thickness). The flame ionization detector (FID) was operated at 350 °C and an integrator (Data Jet-CH2, Spectra-Physics, San Jose, CA) was used for data acquisition. The capillary column was held at a constant temperature of 100 °C. The carrier gas was carbon dioxide (SFC/SFE grade, Air Products, Allentown, PA). The column pressure program utilized was as follows: an isobaric hold at 10.1 MPa for 5 minutes, then increased to 24.2 MPa at 0.404 MPa min^{-1}, followed by another increase to 32.3 MPa at 1.01 MPa min^{-1}.

GC-FAME analyses were performed according to previously described methods[28] on a HP5890 Series II GC using a FID

detector (Hewlett Packard Company, Wilmington, DE) and a 100% poly(biscyanopropylsiloxane) column (SP-2340, Supelco, Inc., Bellefonte, PA, 60 m × 0.25 mm, 0.20 µm thickness). The GC oven parameters were modified slightly for better separation of the standards. The oven was held at 100 °C for 5 minutes, then increased to 190 °C at 3 °C min^{-1}, then increased at 1 °C min^{-1} to 200 °C and held for 15 minutes, followed by a final increase at 50 °C min^{-1} to 250 °C, where it was held for 1 minute. GC-MSD (mass selective detector) analysis of the FAMEs were performed on a HP5890 Series II Plus GC interfaced with a HP5971A MSD using the same column as described above. The precision of the FAME analysis was 0.1% relative standard deviation.

For a typical reaction, the oven was set to a temperature between 250–340 °C, the water pump was then set to a constant flow of 2.0 mL min^{-1}, and then water flow was commenced as the oven was heated. The back pressure regulator was set for an overall system pressure of 15.2 MPa (just enough pressure to keep the water from boiling) and the cooling bath was operated at 80 °C. Once the water had reached the desired temperature, the oil pump was set to a constant flow of 0.4 mL min^{-1} and oil pumped into the system, yielding a total flow in the system of 2.4 mL min^{-1}, and approximately a 15 minute residence time in the reaction chamber. After hydrolysis, the water–oil stream was cooled and depressurized, and collected in a beaker, to which sodium chloride had been added to break any emulsions that formed. The oil was initially pumped into the reactor for approximately 30 minutes before being shut off. However, the flow of water was allowed to continue until there was no visible oil/product being collected, at which time, the reaction was stopped.

The resultant water–product mixture was separated by pouring the mixture into a separatory funnel and extracting with diethyl ether. The ether was then evaporated to leave an oil or a solid consisting of the hydrolyzed fatty acids and any unreacted triglycerides. This extract was then subjected to SFC to determine the degree of hydrolysis. GC-FAME analysis was then utilized to determine if the triglyceride-derived fatty acid composition had been altered during the reaction.

In some experiments, a view cell was placed downstream rather then the tubular reactor. This was contained in an GC oven, that had been modified to include a window in the oven door, for viewing the cell. The view cell consisted of a 316 SS chamber (*ca.* 59 mL volume), tempered transparent glass, and grafoil gasket, (Model 17-R-40, Jergunson Gage and Valve, Strongsville, OH). The cell had a recommended rating of 22.2 MPa at 316 °C for liquids under pressure and a 3.03 MPa rating for steam. We exceeded this maximum temperature rating, but only with extreme caution, and at a reduced pressure relative to its maximum rating (152 MPa at 340 °C), making sure that the cell contents always remained in the liquid state. Residence times of the oil mixture in the high pressure view cell and the unpacked tubular reactors was calculated from a knowledge of the total metered flow rates through the devices. In the case of the view cell, individual segments of emulsified fat were timed during transit through the cell and gave good agreement with those calculated from flow rate measurement.

Acknowledgments

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Aldehyde allylation

in liquid carbon dioxide

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Summary

Various aldehydes react with allyl bromide mediated by indium in liquid carbon dioxide to give homoallylic alchohols.

Introduction

In recent years, owing to an increased awareness of the detrimental effects that organic solvents have on the environment, a substantial amount of research has been devoted to exploring chemistry that is more environmentally friendly.[1] A large part of this endeavor concerns itself with solvents. Almost all chemical processes make use of organic solvents at some point. These organic solvents, used in academic research and in industry, are often very harmful to the environment, and as a result are frequently subject to government restrictions and high waste disposal costs. Consequently, methods that successfully minimize their use are the focus of much attention. Among our efforts at finding alternative media for organic reactions, we explored the feasibility of conducting indium mediated allylation of aldehydes using liquid carbon dioxide as the solvent.

Results and discussion

We initially had considered attempting the allylation in supercritical CO_2. Despite an established history as an effective extractor, in recent years attention has been paid to the use of supercritical fluids as reaction mediums.[2] CO_2 in particular has emerged as a popular choice for a reaction solvent. It has proven an effective solvent for a number of reactions,[3] including the Diels–Alder reaction,[4] the Pauson–Khand reaction[5] and free radical brominations.[6] However, we quickly became intrigued with the idea of using liquid CO_2 instead. For one thing, the temperatures and pressures required for a liquid phase CO_2 system are mild enough that setting up such a system in the laboratory was quite easy. Various studies[7] attest to the ability of liquid CO_2 to substitute effectively for supercritical CO_2 in different chemical processes. In our research, we found indium metal to be a highly effective mediator in coupling reactions between carbonyl compounds **1** and allyl bromide **2** in liquid carbon dioxide. The reaction went smoothly at room temperature, producing the cross-coupled product **3** exclusively [eqn. (1)].
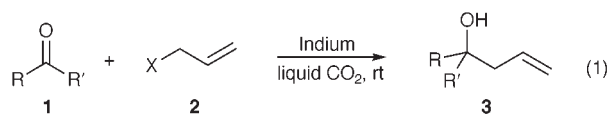
The problem with which we were initially confronted was one of system design. The exigencies of working with a high pressure system imposed certain constraints on the reaction; instead of adding our reactants to the solvent, as is normal in organic chemistry, it was necessary for us to reverse this order. To begin the

reaction, we mixed together in the metal bomb the aldehyde, indium, and allyl bromide, and only then added liquid CO_2 to the system. It had recently been demonstrated by our group that indium promoted the same carbonyl allylation under neat conditions,[8] and there was thus some concern that the allylation reaction would begin before we had even added the liquid CO_2. However, it had also been established in that study that vigorous stirring was necessary to promote the neat allylation, and this presented us with our window of opportunity. While the bomb was filling with liquid CO_2, the entire vessel was completely submerged in an ice-water bath, and this served a two-fold purpose. First, the lower temperature promoted condensation of gaseous CO_2, and second, it was hoped that the lower temperature would help impede any neat reaction of the mixture that might possibly occur. Stirring was started only once the vessel was filled with liquid CO_2.

For the inaugural reaction in this project, we mixed benzaldehyde, allyl bromide, and indium powder in a 10 mL high pressure metal bomb. Liquid CO_2 was added, and the system was stirred 48 h at room temperature. The reaction was worked up with diethyl ether and 1M HCl. After drying over magnesium sulfate

Green Context

In most reactions, the major component is the solvent. Care must therefore be taken to ensure that solvent is chosen to minimise waste generation, both through supporting efficient reaction and facilitating product isolation and solvent recovery. However, the recent increased awareness of the potentially detrimental effects of organic solvents on the environment has led to a rapid growth in research into alternative reaction media. In this respect, supercritical fluids, in particular carbon dioxide, have recently been shown to be excellent for many reactions (see *e.g. Green Chemistry*, 1999, 1, 65 and 261 (preceding paper)). Carrying out reactions in liquified gases under sub-critical conditions can be easier experimentally, and can often have similar benefits—the solvent often has similar properties to the supercritical equivalent, and is separated by depressurisation, ready to be used again. This article describes a clean carbon–carbon bond forming reaction mediated by indium which can be carried out efficiently in liquid carbon dioxide under mild conditions. It is hoped that this breakthrough will encourage more studies of the use of metallic reagants in supercritical carbon dioxide. An alternative procedure to similar products has been described in *Green Chemistry*, 1999, 1, 167.   ***DJM and JHC***

and removing the solvent under vacuum, the ^{1}H NMR spectrum of the crude material indicated that the cross coupling product had been obtained cleanly, with very little unconverted benzaldehyde left over. No by-products were observed in the ^{1}H NMR spectrum of the crude reaction mixture. Subsequent purification of the crude product by flash chromatography afforded the desired product in 82% yield.

Various carbonyl compounds were then allylated in a similar manner (Table 1). For each aldehyde, the reaction proceeded smoothly, providing the resulting alchohol in moderate to good yield. Some of the aldehydes reacted more quickly than others; to ensure completion in each case, the mixtures were generally stirred for 48 hours. Aliphatic (entry 10) and aromatic aldehydes gave similar yields. For the most part, the presence of substituents on the benzene ring did not have an appreciable effect on the yield or rate of the reaction. In nearly all cases, conversions greater than 85% were obtained, in many cases being quantitative. The yields of the different products, however, belie the effectiveness of the reaction. The relatively lower isolated yields do not stem from a limitation on the reaction's part; rather they are the result of the inherently awkward workup (due to the reaction apparatus) in which some of the product is inevitably lost. In all cases, to avoid further neat reaction of the system after the CO_2 was vented, it was necessary to transfer as quickly as possible the reacted mixture to the receptacle where it was worked up. It was sometimes necessary to sacrifice a small amount of the product to facilitate this transfer, and this is reflected in the yields. Simple changes in the design of the liquid CO_2 reaction vessel should surmount these problems.
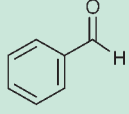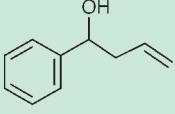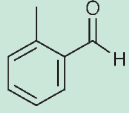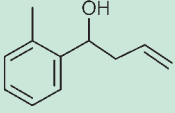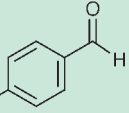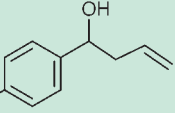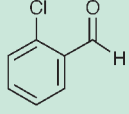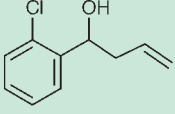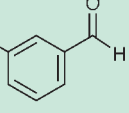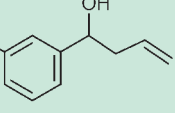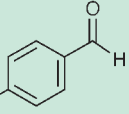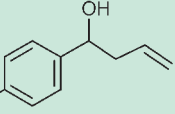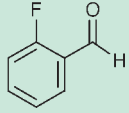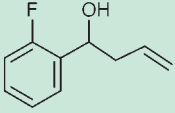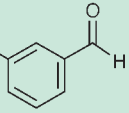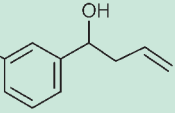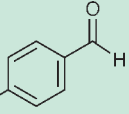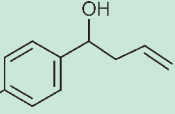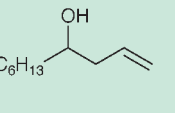
As previously indicated, there was initially some concern that the reaction was taking place while still neat, before the addition of the liquid CO_2. To demonstrate to ourselves that the allylation reaction in liquid CO_2 was indeed occurring in liquid CO_2, we needed to successfully allylate an aldehyde that had proven to be impossible to allylate under neat conditions. A salient limitation on the part of the neat reaction had been its inability to allylate solid aldehydes. Various attempts to perform such an allylation under neat conditions had not been successful. We chose the solid 4-cyanobenzaldehyde as our carbonyl (entry 9). The solid aldehyde was mixed with the reactants, and to the mixture was added a drop of Fomblin$^@$ (MW = 1800), a perfluoropolyether surfactant.[9] Following the same procedure as for the other carbonyls, reaction of the mixture provided the corresponding alchohol in 58% yield. This effectively demonstrated that liquid CO_2 can facilitate reactions impossible under neat conditions.

In summary, the indium mediated-allylation of carbonyl compounds using liquid carbon dioxide as a solvent was shown to be quite effective in most cases. It presents a relatively clean and efficient method of forming homoallylic alchohols. Using liquid CO_2 as a solvent avoids the waste disposal problems associated with organic solvents. In contrast to the corresponding neat allylation, the liquid CO_2 mediated reaction was able to allylate solid aldehydes successfully.

Experimental

A typical experimental procedure: A mixture of benzaldehyde (219 mg, 2.06 mmol), allyl bromide (1.5 equiv., 380 mg, 3.09 mmol), and indium (1.5 equiv., 360 mg, 3.09 mmol) was placed in a 10 mL high pressure metal bomb. The bomb was then connected to a siphon cylinder containing liquid carbon dioxide, placed in an ice water bath, and filled to capacity over about one minute with liquid carbon dioxide at approximately 850 psi. The bomb was then removed from the ice water bath and the mixture

Table 1

Entry	Substrate	Product	Yield(%)
1			81.8
2			45.3
3			74.1
4			57.7
5			56.8
6			55.3
7			37.8
8			68.8
9			57.8
10	$C_6H_{13}CHO$		59.0

was stirred vigorously at room temperature for 48 h. After venting the carbon dioxide from the reaction vessel, the residue was quenched with diethyl ether (5 mL) and 1M HCl (3 mL). The mixture was extracted with ether (3 × 10 mL), and the combined ethereal extracts were washed with water and dried over magnesium sulfate. The solution was then filtered and concentrated under vacuum to produce the crude product, which was subsequently purified by column chromatography, giving the desired 1-phenylbut-3-en-1-ol (282 mg, 82%) as a colourless oil.

Caution: When working with liquid CO_2, care should be taken to minimize the dangers that are associated with such high pressure systems. Among other precautions, a plexiglass shield may be used as protection from any possible explosions. Extra care should also be taken when venting the bomb; releasing the pres-

sure too quickly can result in the sudden expulsion of the system's contents.

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Alkylation of *p*-cresol with methyl *tert*-butyl ether (MTBE)

over a novel solid acid catalyst UDCaT-1

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Summary

A novel mesoporous and strong acid catalyst UDCaT-1 is found to be the most active and selective in comparison with several others in the alkylation of *p*-cresol with MTBE to form 2-*tert*-butyl-*p*-cresol.

Introduction

Butylated hydroxytoluene (BHT) is a well known antioxidant and the basic raw material for the manufacture of oil-soluble phenol-formaldehyde resins.[1] It is conventionally prepared by the acid catalysed reaction of isobutylene with *p*-cresol. The reaction is consecutive with formation of 2-*tert*-butyl-*p*-cresol followed by 2,6-di-*tert*-butyl-*p*-cresol which is popularly called BHT.[1,2] Owing to the problems associated with unavailability, transportation and handling of isobutylene, particularly for use in low-tonnage fine chemical and specialty manufacture, it is advantageous to generate pure isobutylene on site. Two attractive sources of isobutylene are *tert*-butanol and methyl *tert*-butyl ether (MTBE). *tert*-Butanol is available as a byproduct in the ARCO process for propylene oxide. The cracking of MTBE for the generation of isobutylene has been discussed by a number of researchers.[2-4] MTBE is a good source for the generation of pure isobutylene and the by-product, methanol, is also a very important raw material in the chemical industry. On the contrary, the dehydration of *tert*-butanol *in situ* leads to water as a co-product in the alkylation reaction and thus different yields of the alkylated product are expected *vis-à-vis* MTBE as the alkylating agent. Synthesis of MTBE from *tert*-butanol and methanol has been studied in this laboratory using a variety of solid acids.[6,7] Heteropoly acids (HPA) supported on clays have shown superior catalytic activity compared to others in the etherification/*O*-alkylation reactions.[5-10]

Different types of solid acids used for the butylation of *p*-cresol include ion-exchange resins, sulfated zirconia, clays, silica-alumina and γ-alumina.[6] Ion exchange resins, in spite of their good activity, have the severe limitations of temperature instability and loss of acid sites due to leaching. Our earlier studies in the synthesis of BHT have shown sulfated zirconia as a very efficient and reusable catalyst.[5] A number of reports are cited for the alkylation of *p*-cresol with MTBE. Most of the researchers have employed cation exchange resins as catalysts; and the use of molecular sieves for the selective adsorption of methanol formed *in situ* by the cracking of MTBE has been reported.[11] The cation exchangers used for the study include Lewasorb AC-10,[12] Wofatit OK-80,[13] Amberlyst-15[14] and Lewatit SPC 120.[15] The formation of methanol, though it does not deactivate the catalyst,

reduces the number of active sites available for the reaction by occupying them. Haubold *et al.*[13] have suggested the use of gasoline for the removal of methanol from the reaction mixture for the reaction of *m*-cresol with MTBE. Macho *et al.*[15] has suggested the removal of methanol by trapping it at 243 °C. Yadav and co-workers have reported the behavior of HPA supported on K-10 clay, particularly dodecatungstophosphoric acid (DTPA) on K-10 in etherification, alkylation and condensation reactions.[6-10]

It appears that different types of catalysts can be used for the butylation of *p*-cresol with MTBE. The use of mesoporous zeolitic materials was thus envisaged. A mesoporous material with high acidity and surface area should have an immense potential for reactions involving bulky molecules to improve the selectivity of desired products. All crystalline long range mesoporous materials until now reported including the M41S and/or MCM-41 family members are found to have only mild acidity comparable to silica-alumina catalysts. A catalyst prepared in our laboratory with the synergistic combination of hexagonal mesoporous silica (HMS) and sulfate modified zirconia material 'UDCaT-1' was found to have interesting catalytic applications. The present work highlights the superior performance of UDCaT-1 *vis-à-vis* other solid acids in the synthesis of 2-*tert*-butyl-*p*-cresol from *p*-cresol and MTBE including kinetic modeling.

Green Context

The alkylation of aromatic substrates is important in many sectors of the chemical industry. Traditional methods of manufacture based on environmentally hazardous catalysts such as aluminium chloride are increasingly being replaced by more benign alternatives but there remains a great need for new catalysts. Solid acids are especially popular in this context and here we can read about a new material that brings together the advantages of a mesoporous inorganic solid (good thermal stability and molecular diffusion rates) with those of a known strong solid acid. The article describes the use of this new catalyst in the important alkylation of *p*-cresol using MTBE. This offers the additional environmental advantage of using a relatively safe *in situ* source of isobutylene rather than the gas itself. *JHC*

Experimental

Catalysts and chemicals

UDCaT-1, Filtrol-24, K-10, Indion-130 and DTPA/K-10 were used as catalysts. Filtrol-24 was obtained from Engelhardt. K-10 was obtained from Fluka. Indion-130 used was a product of Ion Exchange (I) Ltd. Dodecatungstophosphoric acid (DTPA) supported clay was prepared by a reported method.[6,7]

 p-Cresol was obtained from s.d. Fine Chem Ltd. MTBE was obtained from Albemarle Corporation, USA.

 Zirconium oxychloride dissolved in distilled water was carefully added dropwise to calcined HMS with vigorous mixing. After each small addition of the solution, the solid was partially dried over a boiling water bath. Ultimately, after all the solution had been added, the solid was dried in an oven at 120 °C for 1 h. The dried material was loaded in a reactor and ammonia gas was passed through it for 3 h. The ammoniated sample was washed with distilled water to remove the chloride ions and dried in an oven at 120 °C for 2 h. The sulfation was carried out by passing dilute sufuric acid through the filter paper containing the dried ammoniated solid material. It was dried in an oven for 1 h at 120 °C and calcined at 550 °C for 3 h to give the active catalyst UDCaT-1.[16] Preparation of sulfated zirconia and 20% DTPA/K-10 was carried out according to a well-established procedure in our laboratory.[5,7]

Reaction procedure

All experiments were carried out in a Parr Autoclave (100 ml) equipped with a four-blade-pitched turbine impeller. The temperature was maintained at ± 0.5 °C of the desired value. The instrument was also equipped with a speed regulator that could maintain the speed at ± 5 rpm of the desired value.

 Predetermined amounts of reactants and the catalysts were charged into the autoclave and the temperature was raised to the desired value. Once the temperature was attained, the initial sample was withdrawn. Further samples were drawn at periodic intervals.

 A typical standard experiment contained 0.22 moles (19.61 g) of MTBE, 0.22 moles (24.31 g) of *p*-cresol and 3.5% *w/w* catalyst, based on the reaction mixture. The temperature was maintained at 100 °C and the speed of agitation was 700 rpm.

Analysis

The samples were analysed on a gas chromatograph (Perkin Elmer Model 8500) equipped with a flame ionisation detector. A 2 m × 0.003 m column was used. The stationary phase was 10% OV-17 supported on Chromosorb WHP. The quantitative analysis was done through calibration with standard synthetic mixtures.

Results and discussion

Reaction chemistry and product distribution

Fig. 1 shows the reaction scheme for the alkylation of *p*-cresol with MTBE. This reaction involves two distinct steps, namely, the cracking of MTBE giving methanol and isobutylene and the addition of the isobutylene formed *in situ* with *p*-cresol giving 2-*tert*-butyl-*p*-cresol and 2,6-di-*tert*-butyl-*p*-cresol *via* consecutive reactions. Further, the diisobutylenes and triisobutylenes could be also formed as side products depending on the type of catalysts and reaction conditions. However, product analysis done showed that not all products depicted in the scheme are formed.

 The use of MTBE as a butylating agent is advantageous. MTBE cracking starts beyond 75 °C in a significant way. Whatever isobutylene is generated *in situ* is consumed and no free isobutylene in the gas phase is noticed and no oligomerisation takes place at low temperatures. The co-product methanol is recyclable. In the earlier studies, we had noticed that no *O*-alkyl-
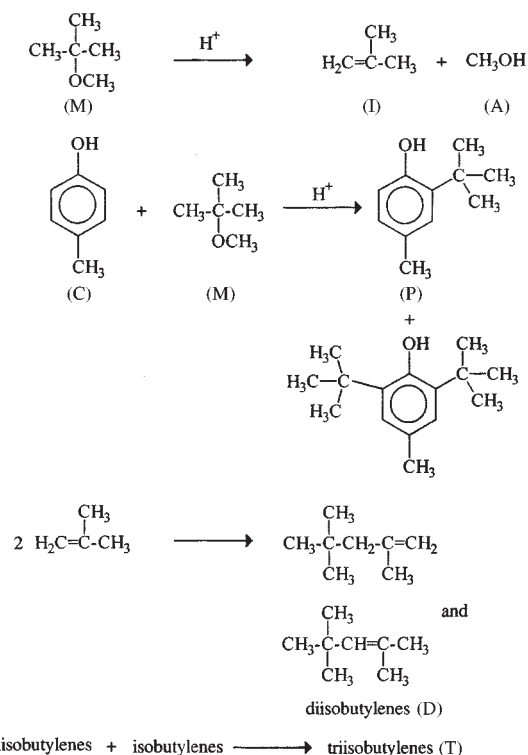

Fig. 1 Reaction scheme

ated product is formed beyond 50 °C when *p*-cersol was alkylated with isobutylene in the presence of sulfated zirconia as catalyst.[5] In the present case, all standard experiments were done at 100 °C and the analysis showed no *O*-alkylated product was formed. The selectivity of *p*-cresol to 2-*tert*-butyl-*p*-cresol was >95% with all catalysts (Table 1). In the case of MTBE as alkylating agent the conversion of *p*-cresol with 1:1 mole ratio was limited to less than 50% in order that the isobutylene formation was not excessive to produce the oligomers. The diisobutylene and triisobutylene content was less than 1% at 100 °C. At higher temperatures the oligomerisation reactions were significant resulting in up to 10% oligomerisation products.

Table 1 Activity of various catalysts for the alkylation of *p*-cresol with MTBE

| Catalyst	% Conversion	% Selectivity to 2-*tert*-butyl-*p*-cresol
1. UDCaT-1	45	97
2. Indion 130	39	92
3. Filtrol-24	19	96
4. Sul. Zirconia	15	91
5. K-10	12	96
6. DTPA/K-10	30	96

MTBE (220 mmol), *p*-cresol (220 mmol); Catalyst loading = 3.5% of reaction mixture; *T* = 100 °C; Speed = 700 rpm; Reaction time 3 h; By-products formed are isobutylene, diisobutylene, triisobutylene and methanol.

 In this work the performance of various solid acid catalysts was evaluated *vis-a-vis* UDCaT-1 catalyst in the absence of mass transfer resistance. These catalysts includes Indion 130 (an ion exchange resin), Filtrol-24 clay, sulfated zirconia, K-10 clay, 20% dodecatungstophosphoric acid (DTPA) on K-10 clay. All

experiments were done in the absence of any mass transfer limitations. Table 1 gives the conversion of *p*-cresol and selectivity to 2-*tert*-butyl-*p*-cresol.

All catalysts give very high selectivity of the mono-alkylated product but the conversion is very high with UDCaT-1. As is evident from Table 1 apart from UDCaT-1, the ion exchange resin catalyst Indion 130 and DTPA/K-10 give a reasonably good conversion of *p*-cresol and very good selectivity to 2-*tert*-butyl-*p*-cresol. Isobutylene could also form diisobutylenes and tri-isobutylenes. However, UDCaT-1 is the best catalyst. In addition to the alkylation with *p*-cresol, there was *in situ* generation of isobutylene *via* cracking of MTBE. A good cracking catalyst and a poor alkylation catalyst would result in loss of the generated isobutylene. A reverse phenomenon would result in poor yield of the required product. It was therefore necessary that the best catalyst should give a reasonable activity for the cracking of MTBE as well as the alkylation of isobutylene with *p*-cresol.

Fig. 2 shows *p*-cresol conversion with time for the various catalysts employed in the reaction. Cracking of MTBE almost
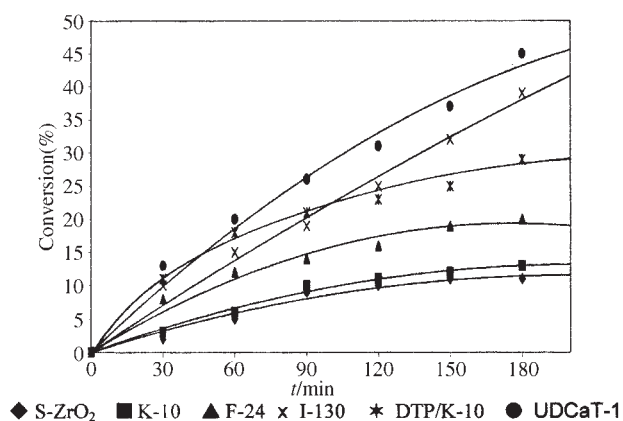
Fig. 2 Effect of different catalysts. *p*-cresol:MTBE = 1:1; Catalyst loading = 3.33×10^{-3}; Speed of agitation = 700 rpm; *T* = 100 °C.

occurred immediately for all the catalysts at the set temperature. Gas chromatographic analysis showed the presence of methanol even at zero time. Consequently isobutylene generation was also instantaneous. Thus the isobutylene formed was available to react with the *p*-cresol to give the desired products. Sulfonated ion exchange resins are well known commercial catalysts that work well for a number of reactions. However, they cannot be used for any reaction above 120 °C. For the alkylation of *p*-cresol with MTBE, Indion-130 gave a conversion of 39% under otherwise similar conditions which was lower than UDCaT-1. The selectivity towards 2-*tert*-butyl-*p*-cresol was 92%, a little lower than the other catalysts employed for the reaction.

Filtrol-24 is another commercially available clay catalyst. The amount of residual acidity in Filtrol is relatively high in comparison with K-10. Since both have similar surface areas (320 m² g⁻¹), Filtrol-24 is expected to give higher activity for the reaction in comparison to K-10. Consequently, Filtrol-24 was found to give the higher conversion (19%) compared to 12% with K-10. Both the clay catalysts gave similar selectivities of 96%. Another interesting observation in the use of K-10 was its very high activity towards the cracking of MTBE. Substantial formation of methanol was observed in the first half hour of the reaction. This could possibly be due to the selective adsorption of MTBE onto the catalyst surface that could be responsible for such a phenomenon.

Our laboratory has studied in detail the activity of superacidic sulfated zirconia and 20% DTPA/K-10 in the alkylation of *p*-cresol with isobutylene, either generated *in situ* or as the pure gas.[10,11] They have reported that 2-*tert*-butyl-*p*-cresol attains a maximum during the course of the reaction after which it gets further alkylated to the dialkylated product. However, for the alkylation of *p*-cresol with MTBE in the current studies sulfated zirconia gave a very low activity. Even the cracking of MTBE proceeded very slowly as was deduced by the formation of methanol. Effects of different parameters were studied under otherwise similar conditions with UDCaT-1 as the catalyst.

Reusabitlity of UDCaT-1
Since UDCaT-1 is a newly developed catalyst, it was essential to conduct studies on its reusability. At the end of the reaction, the catalyst was filtered off and used as such in subsequent reactions. Fig. 3 shows the reusability of the catalyst for three runs. The conversions are marginally lower by 5% from the previous use.
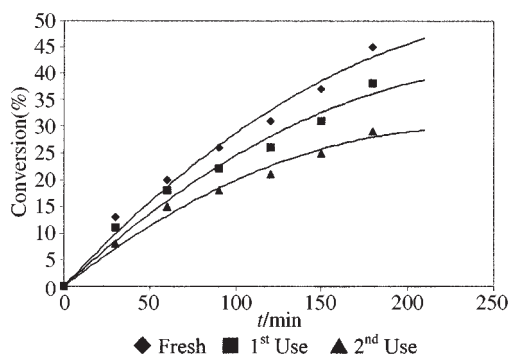

Fig. 3 Reusability of catalyst. *p*-Cresol:MTBE = 1:1; Catalyst loading = 3.33×10^{-2} g cm⁻³; Catalyst = UDCaT-1; *T* = 100 °C.

Since the particles were fine some losses due to attrition were responsible for this. On unit weight basis of the actual catalyst present in the reaction under otherwise similar conditions the reusability of catalyst is satisfactory.

Effect of speed of agitation
The reaction was studied at different speeds of 700, 800 and 1000 rpm, keeping all other parameters constant. There was no observed change in the rate of reaction. It was therefore concluded that there were no external mass transfer resistance controlling the reaction at or above 700 rpm (Fig. 4). All further runs were carried out at 700 rpm.
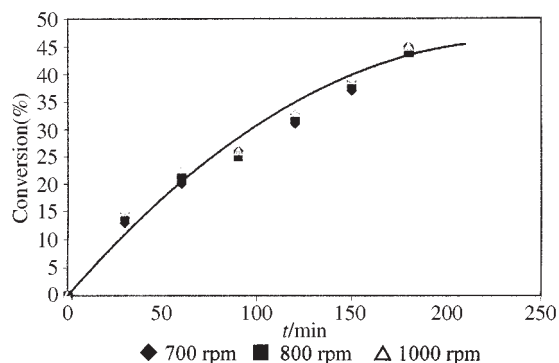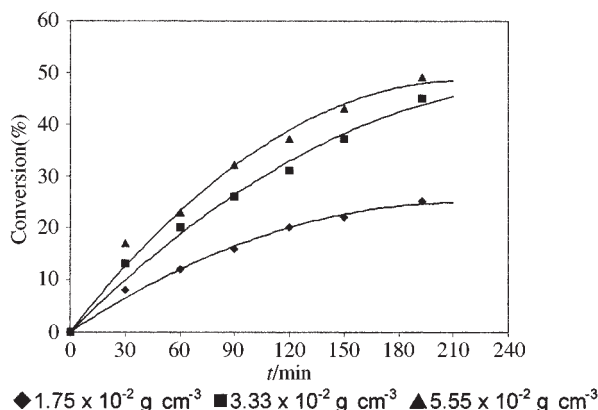

Fig. 4 Effect of speed of agitation. *p*-Cresol:MTBE = 1:1; Catalyst loading = 3.33×10^{-2} g cm⁻³; Catalyst = UDCaT-1.

Effect of catalyst loading

Fig. 5 shows the plot of conversion of *p*-cresol with time at different catalyst loading. The rate of reaction increases with the increase in catalyst loading. With an increase in catalyst loading,
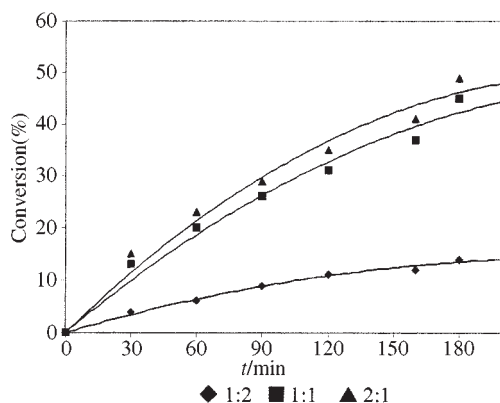

Fig. 5 Effect of catalyst loading. *p*-Cresol : MTBE = 1 : 1; Catalyst = UDCaT-1; Speed of agitation = 700 rpm; T = 100 °C.

the number of accessible active sites for catalysing the reaction increases. With regards to selectivity there was a negligible difference in selectivity profiles of the products at catalyst loadings of 1.5 and 6% of the total mass of the reactants (*i.e.* 1.75–5.55 × 10^{-2} g cat cm^{-3} liquid phase). The figure shows that with an increase in the catalyst loading from 1.5–3%, there is a marginal increase in the reaction rates but from 3–6% there is a substantial increase. This is because, in addition to the increase in the number of active sites, the turnover number of products also increases, resulting in the quicker consumption of *p*-cresol and the formation of products.

Effect of mole ratio of reactants

Fig. 6 shows the plot of conversion *vs.* time with mole ratios of 1 : 1, 2 : 1 and 1 : 2 of *p*-cresol to MTBE. It was ensured that the

Fig. 6 Effect of mole ratio. *p*-Cresol : MTBE; Catalyst loading = 3.33 × 10^{-2} cm^{-3}; Catalyst = UDCaT-1; Speed of agitation = 700 rpm; T = 100 °C.

concentration of the catalyst was kept constant at the different mole ratios. A marked difference in the rate of reaction was observed when the concentration of either of the reactants was changed. The rate of reaction as a function of the mole ratio followed the trend 2 : 1(highest) > 1 : 1 > 1 : 2 of *p*-cresol to MTBE. If this process was a conventional homogeneous reaction the rate of reaction would have increased with the increase in the isobutylene concentration. In the latter case where the isobutylene generated is much higher the observed conversion of *p*-cresol is still lower. In a heterogeneous system this may be due to the fact that the isobutylene generated is strongly and preferentially adsorbed on the catalytic sites resulting in a low conversion of *p*-cresol.

Effect of temperature

Fig. 7 shows the plots of conversion of *p*-cresol *vs.* time at 80, 100 and 115 °C. As expected the rate of reaction increases with
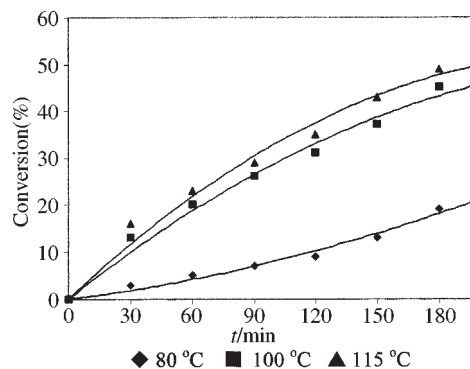
Fig. 7 Effect of temperature on conversion. *p*-Cresol : MTB = 1 : 1; Catalyst loading = 3.33 × 10^{-2} g cm^{-3}; Catalyst = UDCaT-1; Speed of agitation = 700 rpm.

increase in temperature. Another important factor is that the selectivity towards 2-*tert*-butyl-*p*-cresol decreases with an increase in temperature, due to the increased rate of reaction towards the formation of 2,6-di-*tert*-butyl-*p*-cresol. Selectivity towards 2-*tert*-butyl-*p*-cresol at 80, 100 and 115 °C was 100, 97 and 91% respectively, *i.e.*, only at temperatures above 100 °C, is the selectivity towards 2-*tert*-butyl-*p*-cresol somewhat decreased.

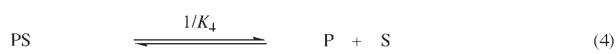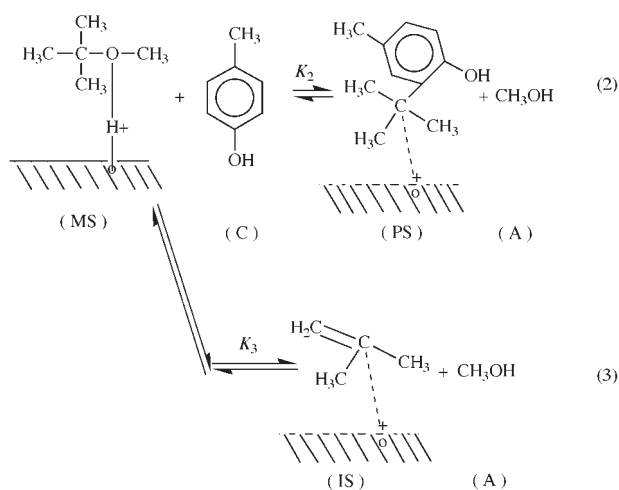## Reaction mechanism and kinetics

Model development

Several mechanisms were considered and the following was found to describe the results. No dehydration of *p*-cresol was found to take place to give the corresponding ether or for that matter no *O*-alkylated product (*p*-cresyl methyl ether) was formed with methanol. This would suggest that there is adsorption of MTBE on the catalytic site which can react with *p*-cresol either from the adjacent site, or MTBE first gets cracked to isobutylene which is then readsorbed on the catalytic site to react with *p*-cresol. Yadav and Thorat [5] have shown that *p*-cresol reacts with isobutylene according to the Eley-Rideal mechanism with sulfated zirconia as a catalyst. Since UDCaT-1 was based on sulfated zirconia and HMS, the same mechanism was assumed to hold and it was found to be in consonance with the experimental data. The O atom of MTBE coordinates with the acid centre of the catalyst designated as H⁺ forming a surface complex.

Adsorption of MTBE (M) on a general catalytic site (S) leads to the formation of adsorbed species MS as shown in eqn. (1)

$$M + S \xrightleftharpoons{k_1} MS$$

K_1 = Adsorption equilibrium constant
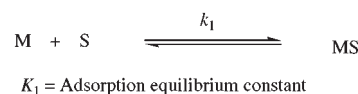
Chemisorbed MTBE (MS) reacts with *p*-cresol (C) from the liquid phase near the site according to the Eley-Rideal mechanism to form the surface species PS of the 2-*tert*-butyl-*p*-cresol (P) and free methanol (A) [eqn. (2)]. The chemisorbed MS can

(2)

(3)

$$PS \xrightarrow{1/K_4} P + S \qquad (4)$$

$$IS \xrightarrow{1/K_5} I + S \qquad (5)$$

$$IS + I \xrightarrow{K_6} DS \qquad (6)$$

$$DS + I \xrightarrow{K_7} TS \qquad (7)$$

$$DS \xrightarrow{1/K_8} D + S \qquad (8)$$

$$TS \xrightarrow{1/K_9} T + S \qquad (9)$$

undergo simultaneous cracking to give isobutylene (IS) and methanol (A) [eqn. (3)]. Isobutylene is also capable of undergoing dimerisation (D) and trimerisation (T) as shown below by eqns. (6) and (7).

If the surface reaction is the rate-controlling step, then the rate of reaction of MTBE is equal to the rate of formation of the alkylated product plus the rate of formation of isobutylene.

If reactions (2) and (3) occur simultaneously then, rate of reaction of MTBE, with the surface reaction step controlling, will be

$$r_M = k_2 C_{MS} C_C - k_{-2}{}^I C_{PS} C_A + k_3 C_{MS} - k_{-3}{}^I C_{IS} C_A \quad (10)$$

If the fractional coverage of catalysts is given by that of MTBE alone, then the rate of reaction of MTBE is given by

$$r_M = \frac{w[k_2 K_1 C_M C_C - k_{-2} K_4 C_P + k_{-3} K_1 C_M - k_3{}^I K_5 C_j]}{(1 + K_1 C_M)} \quad (11)$$

where w is the catalyst loading.

When the reaction is far away from equilibrium, then rate of reaction of MTBE is given by

$$r_M = \frac{[k_2 K_1 C_M C_C + k_3 K_1 C_M]w}{(1 + K_1 C_M)} \quad (12)$$

In the case of weak adsorption of all species including MTBE

$$K_1 C_M \ll 1$$
$$r_M = [k_2 K_1 C_M C_C + k_3 K_1 C_M]w \quad (13)$$

The selectivity to alkylated product is given by the ratio of the formation of P and that of isobutylene (I)

$$S_{P/I} = \frac{k_2 C_C}{k_3} \quad (14)$$

The selectivity depends only on the concentration of *p*-cresol and the ratio of rate constants k_2/k_3

The rate of reaction of *p*-cresol leading to 2-*tert*-butyl-*p*-cresol is given by eqn. (15)

$$r_C = -dC_C/dt = [k_2 K_1 C_M C_C]w \quad (15)$$

which is a typical second order reaction. For equimolar concentrations of C_M and C_C at zero time, eqn. (15) can be written in terms of fractional conversion of *p*-cresol and integrated to get eqn. (16).

$$\left| \frac{X_C}{1 - X_C} \right| = C_{CO} w k_2 K_1 t$$
$$= C_{CO} w k t \quad (16)$$

where $k = K_1 k_2$, rate constant

A plot of $X_C/(1 - X_C)$ *vs.* t should give the slope equal to $C_{CO} w k$ from which k can be calculated.

When the initial concentration of MTBE and *p*-cresol are different, let M_R be the mole ratio $M_R = C_{CO}/C_{MO}$, ratio of initial concentration of *p*-cresol to that of MTBE. On substitution, eqn. (15) can be integrated to give eqn. (17).

$$\ln \left| \frac{(M_R - X_C)}{M_R(1 - X_C)} \right| = C_{CO}(M_R - 1)w k t \quad (17)$$

Where $M_R \neq 1$

A plot of left hand side of eqn. (17) *vs.* time could give a slope equal to $C_{CO}(M_R - 1)wk$ from which k could be calculated.

Reaction kinetics

It was found that the weak adsorption of all species on the catalytic sites was valid wherein the surface reaction between adsorbed MTBE with *p*-cresol from the liquid phase, according to the Eley-Rideal mechanism controlled the overall rate of reaction [eqn. (2)]. Thus, eqn. (16) for equimolar concentrations of MTBE and *p*-cresol, and eqn. (17) for non-equimolar concentrations, respectively should be only considered.

Plots of $X_C/(1 - X_C)$ *vs.* time were made for equimolar concentration ($M_R = 1$) of C_M and C_C for three different catalyst loadings (w) as shown in Fig. 8, showing a linear relationship as per
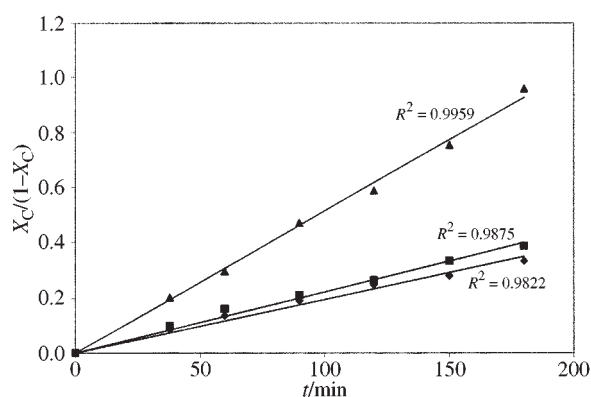
Fig. 8 Plot of $X_C/(1 - X_C)$ *vs.* time at different catalyst loading. *p*-Cresol : MTBE = 1 : 1; Catalyst = UDCaT-1; Speed of agitation = 700 rpm.

the model [see eqn. (16)]. The slopes of these plots are equal to $C_{CO}wk$. The linear regression (best-data fit) shows the R^2 values

as 0.9822, 0.9875 and 0.9959 for catalyst loadings of 1.75×10^{-2}, 3.33×10^{-2} and 5.55×10^{-2} g cm^{-3}, respectively. This is an excellent match with theory. The k values are calculated as 0.364, 0.233 and 0.399 cm^6 g^{-1} mol^{-1} s^{-1} respectively giving an average value of 0.332 cm^6 g^{-1} mol^{-1} s^{-1}.

Plots of $\ln[M_R - X_C/M_R(1 - X_C)]$ $vs.$ time were made for non-equimolar concentrations of C_M and C_C ($M_R = 2$ and 0.5) as shown in Fig. 9 and the best fit data show the R^2 values of 0.9875
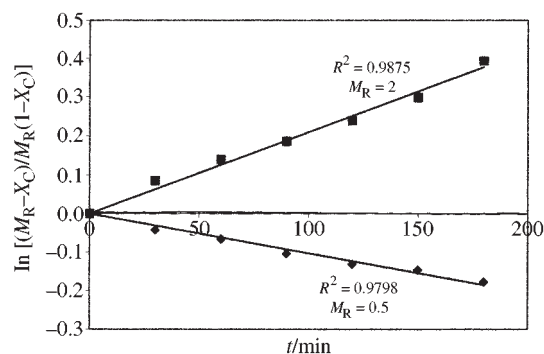
Fig. 9 Plot of $\ln[M_R - X_c)/M_R(1 - X_c)]$ $vs.$ time. $M_R = p$-Cresol:MTBE; Catalyst loading $= 3.33 \times 10^{-2}$ g cm^{-3}; Catalyst $= $ UDCaT-1; Speed of agitation $= 700$ rpm.

and 0.9798 which again validates the model. The slope of these plots is $C_{CO}(M_R - 1)wk$, from which the average k was obtained as 0.3333 cm^6 g^{-1} mol^{-1} s^{-1}

Conclusions

UDCaT-1 was found to be a highly active and selective catalyst for the alkylation of p-cresol with MTBE leading to 2-$tert$-butyl-p-cresol. Among other catalysts ion exchange resins Indion-130 was the second best catalyst. The high acidity and controlled activity of UDCaT-1 makes it an attractive catalyst. It is recyclable and being an inorganic solid it can be employed at higher temperatures in comparison to ion exchange resin catalysts. The kinetic model was developed according to which MTBE gets adsorbed on the catalyst site to react with p-cresol (Eley-Rideal mechanism).

Acknowledgments

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Paper 9/06724H

Clean synthesis of adipic acid

by direct oxidation of cyclohexene with H_2O_2 over peroxytungstate–organic complex catalysts

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Summary

Direct catalytic oxidation of cyclohexene to adipic acid with hydrogen peroxide over environmentally benign peroxytungstate–organic complex catalysts is performed with excellent yields and selectivities, without any organic solvent and harmful phase-transer catalyst.

Introduction

Environmental legislation and increasing public awareness of environmental issues are providing an ever-increasing need for the introduction of clean syntheses to replace traditional chemical manufacturing. An effort to cleanly synthesise adipic acid, which has been manufactured using nitric acid oxidation of cyclohexanol or cyclohexanone in most current industrial processes, has been made recently.[1–4] Research on the clean synthesis of adipic acid has also been reported recently,[5] in which cyclohexene could be efficiently oxidized to adipic acid with aqueous 30% H_2O_2 in the presence of small amounts of Na_2WO_4 and $[CH_3(n\text{-}C_8H_{17})_3HSO_4$ as a phase-transfer catalyst. The $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$ as a phase-transfer catalyst is, however, relatively expensive if it is used in industry for adipic acid production, and quaternary ammoniums are generally not environmentally benign. Here we report a cheaper and environmentally benign peroxytungstate–organic complex which could be used as a highly efficient catalyst for the direct catalytic oxidation of cyclohexenes to adipic acid with hydrogen peroxide without any phase-transfer catalyst.

Results and discussion

The experimental results indicated that the organic acids as ligands have strong impact on the catalytic oxidation (Table 1). The cyclohexene conversion and the selectivity for adipic acid was 97.3 and 38.9% respectively if the peroxytungstate was only present in the reaction media. However, the selectivity for adipic acid could be greatly enhanced when both peroxytungstate and organic acids were present in the reaction media. The best catalytic performance could be achieved when oxalic acid was used as ligand, *i.e.* in addition to complete conversion of cyclohexene, 96.6% selectivity for adipic acid was obtained. The main byproducts were cyclohexanediol and pentanedioic acid. In comparing the relationship between the complex catalyst performance and the acidities and molecular structures of the organic acids as ligands listed in Table 1, it can be seen that: (1) The stronger the acidity of the organic acid, the higher yield and selectivity for apidic acid could be obtained. Since an acidic environment is essential for an oxidation reaction involving H_2O_2 as oxidant,[6] and the acidity in this reaction media was derived from the organic acids, the acidity of the reaction media would directly depend upon the acidity of the organic acids. (2) The catalytic activities of the peroxytungstate–organic complexes with a monochelate ring were higher than that with double or multiple chelate rings. For example, the acidity of tartaric acid is stronger than that of succinic acid, 1, 5-pentanedioic acid and salicylic acid, the catalytic activity, however, was relatively lower. This is probably due to the formation of multiple chelate rings between peroxytungstate and tartaric acid, which would reduce the number of peroxy species bonded to tungsten. (3) The yields and selectivities of peroxytungstate complexed with pentanedioic acid or 8-hydroxyquinoline were respectively higher than that with succinic and nicotinic acids, although the acidities of pentanedioic acid and succinic acid, or 8-hydroxyquinoline and nicotinic acid are quite similar. These may be related to the different oleophilic properties of these organic acids. Since the peroxytungstate was only water-soluble but immiscible with cyclohexane, it must penetrate from the aqueous H_2O_2 phase into the 'oil phase' before initiating oxidation of cyclohexene. When the peroxytungstate was complexed with the organic acids, the resultant catalyst system not only possessed the capability of carrying active oxygen species but also became oleophilic, and the more oleophilic a peroxytungstate–organic complex (*i.e.* more –CH2– units in the structure), the better catalyst performance is.

The pioneering works by Ishii *et al.*[7] indicated that the oxidation virtually did not occur with H_2WO_4 in water. This is probably because the cyclohexene is immiscible with water and the H_2WO_4 is only water-soluble. When the peroxytungstate was complexed with the organic acids, the resultant catalyst system not only possessed the capability of carrying active oxygen species but also became oleophilic, therefore, a very good catalyst system for the oxidation of cyclohexene could be formed.

Since the best yield and selectivity could be achieved with the peroxytungstate–oxalic acid catalyst system, the effect of the amount of catalyst on the formation of adipic acid was further investigated. The experimental results showed that the oxidation

Green Context

Millions of tonnes of adipic acid are produced each year for the manufacture of nylon-6. The conventional method for the production of adipic acid involves oxidation of cyclohexane to cyclohexanol (a step which shows poor selectivity), followed by nitric acid oxidation. This report describes a clean and direct catalytic method for the conversion of cyclohexene to adipic acid.

*Stewart J. Tavener, University of York*

Table 1 Influence of organic acids as ligands on the catalyst performance in cyclohexene oxidation[a]

	Products (wt%)[b]						
Ligand	(cyclohexene)	(diol, OH, OH)	(O, OH)	(O, O)	(CO₂H, CO₂H glutaric)	Others	(CO₂H, CO₂H adipic)
Oxalic acid	—	1.2	—	—	—	1.6	96.6
Succinic acid	—	0.2	—	—	4.2	1.5	94.0
Pentanedioic acid	—	0.2	0.1	—	3.6	1.0	95.1
Salicylic acid	—	4.7	0.7	—	—	4.5	90.1
Nicotinic acid	—	4.6	2.9	0.5	—	2.2	89.8
8-Hydroxyquinoline	—	5.8	0.8	0.5	—	2.2	90.7
Tartaric acid	—	1.7	1.1	—	—	16.6	80.6
—	2.7	39.8	—	—	—	18.6	38.9

[a] *Reaction conditions*: catalyst 1.0 mol% (relative to 0.3 mol cyclohexene), 30% H_2O_2 (134 ml), refluxed and stirred for 24 h.
[b] Other by-products were valeric acid, cyclopentanone and cyclohexanone.

Table 2 Influence of the amount of peroxytungstate–oxalic acid complex catalyst on the catalystic performance in cyclohexene oxidation[a]

|		Products (wt%)				
Amount of catalyst (mol%)	Reaction time/h	(diol, OH, OH)	(O, OH)	(CO₂H, CO₂H glutaric)	Others	(CO₂H, CO₂H adipic)
0.5	24	6.6	0.5	3.5	3.5	86.0
1.0	24	1.2	—	—	1.6	96.6
1.5	8	2.3	0.3	3.4	1.9	93.5
2.0	8	0.9	—	3.7	1.1	94.2
2.5	8	0.6	0.1	1.9	1.6	95.8

[a] Reaction conditions same as in Table 1.

reaction has to be conducted for 24 hours in order to achieve complete cyclohexene conversion and more than 90% of adipic acid selectivity when the amount of the catalyst charged was <1.5% mol (relative to the amount of cyclohexene), Table 2. However, 93.5% yield or selectivity for adipic acid could be achieved when the amount of the catalyst was increased to ≥1.5% (mol). It is worth mentioning that such yield and selectivity was the same as that obtained from the Na_2WO_2 and $[CH_3(n-C_8H_{17})_3N]HSO_4$ catalyst system reported recently by Sato *et al.*[5] This means that the expensive $[CH_3(n-C_8H_{17})_3N]HSO_4$ PTC could be replaced by a much cheaper and simpler organic acid, *e.g.* oxalic acid, without any loss of yield and selectivity for adipic acid production, and moreover, the catalyst system itself is more environmentally friendly.

We are currently investigating the possibility of recovery and reusing the catalyst, and using oxygen or air to replace some of the H_2O_2.

Experimental

The peroxytungstate–organic complex was prepared *in situ* by adding Na_2WO_4·$2H_2O$ (2.74 g, 7.5 mmol) and organic acids (7.5 mmol equiv.) and aqueous 30% H_2O_2 (134 ml, 1.32 mmol) into a 250 ml round-bottomed flask equipped with a mechanical stirrer, a flux condenser and a thermometer. The mixture was stirred at room temperature for *ca.* 15 min and the resultant solution changed from light yellow to orange, indicating the formation of a peroxytungstate–organic acid complex, *i.e.* $[W(O)(O_2)_2L_{(2)}]^{2-}$ ($L_{(2)}$ is an organic acid with double or multi functional groups), **1**. Cyclohexene (24.9 g, 0.3 mmol, H_2O_2: cyclohexene = 4.4:1) was added into the above solution. The mixture was initially heated at 72 °C for 3–4 h
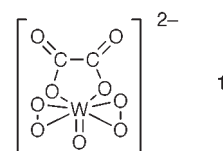
and then at 94 °C for 4–20 h with stirring at *ca.* 1000 rpm. The reaction was then stopped and the resultant aqueous mixture was cooled at 0 °C overnight. A white crystalline solid, apidic acid, separated out and was filtered off and after washing and drying had purity ≥99% (GC analysis) and mp 151–152 °C. Some extra apidic acid product could be obtained if the remainder mother liquor was further evaporated. The best total yield of apidic acid was 93–95%.

After each reaction, the resulting aqueous mixture containing reactant and products was directly analyzed with HP6890/5973 GC-MS with crosslinked 5% PH ME Siloxane column, 30 m × 0.25 mm × 0.25 μm.

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Synthesis of antisense oligonucleotides

using environmentally friendly and safe deprotection procedures

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Summary

It is demonstrated that mixed-sequence phosphorothioate oligodeoxyribonucleotides can be synthesized on scales up to 80 mmol without using chlorinated solvents like dichloromethane, while preserving both high yield and purity of the product. A solution of dichloroacetic acid in toluene cleanly and efficiently removes 4,4′-dimethoxytrityl groups from the 5′-terminus of the growing oligonucleotide chain during synthesis on the solid support. Aqueous ammonia treatment at room temperature at atmospheric pressure furnishes deprotected oligonucleotides reducing the risk that pressurized reaction glass vessels pose. To ensure facile separation of polymer beads (Primer HL 30) and oligonucleotide solution, minimum agitation of the reaction mixture is applied.

Introduction

Oligonucleotides and their analogs are finding widespread application in diagnostics, molecular biology, and as therapeutic agents. Phosphorothioate oligonucleotides in particular, in which a nonbridging oxygen atom of the natural phosphate diester linkage is replaced by sulfur, have emerged as drugs for treatment of disease through an antisense mechanism of action.[1] With the first antisense therapeutic agent approved[2] by the US Food and Drug Administration for marketing in 1998 and with several other antisense oligonucleotides currently under clinical or preclinical evaluation, the development of safe and economical methods for the synthesis of high-quality oligonucleotides at large scale has become a major focus of our research.[3] Typically, synthesis of oligonucleotides at scales up to 150 mmol is performed in a cyclic manner on automated solid phase synthesizers using phosphoramidite derivatives of protected nucleosides with 4,4′-dimethoxytrityl (DMTr) protection of the 5′-hydroxy group, benzoyl protection for adenine (dA^{bz}) and cytosine (dC^{bz}) and isobutyryl for guanine (dG^{ib}).[4] Deprotection of oligonucleotides is the focus of the work reported here.

Removal of the acid-labile 5′-O-DMTr protecting group from support-bound oligonucleotide plays a role in each cycle (Scheme 1) that is crucial to high product yield and quality.[5] Although several reagents have been developed for DMTr removal from nucleosides,[6] many have limited applicability to automated oligonucleotide synthesis on solid supports. The most commonly used reagents today are dilute solutions (2–15%) of an
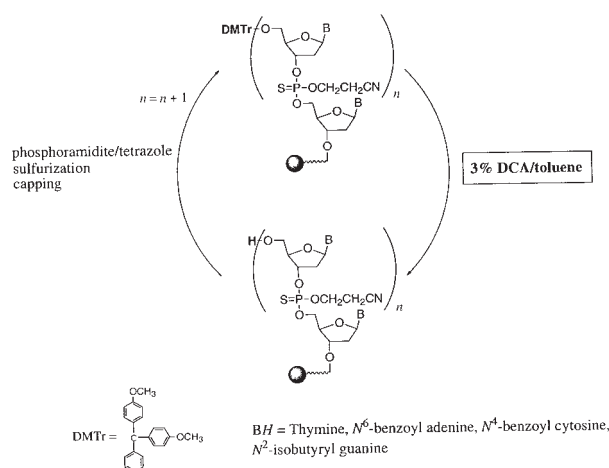
Scheme 1

organic acid like trichloroacetic acid (TCA, pK_a 0.8) or dichloroacetic acid (DCA, pK_a 1.5) in a halogenated solvent, typically dichloromethane. The high volatility (vapor pressure 380 mm at 22 °C) of dichloromethane and its high toxicity and carcinogenicity pose personnel and environmental hazards resulting in stringent regulation, for example, by the

Green Context

Oligonucleotides and their analogues are now being widely used in various applications including therapeutic agents and diagnostics. A key step in their synthesis is the removal of an acid-labile protecting group and this procedure needs to be suitable for modern automated synthesis on solid supports. Unfortunately the most effective methods are based on halogenated solvent systems which are increasingly becoming environmentally unacceptable and hazardous pressurised reactors. In this article, a new environmentally friendly and safe deprotection procedure is reported. The method is based on a hydrocarbon solvent and also furnishes the desired oligonucleotides without the need for hazardous pressure vessels. *JHC*

Occupational Safety and Health Administration.[7] As oligonucleotide synthesizers are now available for syntheses up to 0.2 mol scale,[8] the quantities of chlorinated waste generated have become quite large, raising issues for safe handling and disposal of large volumes. Disposal of halogenated solvents is particularly expensive. We were interested in replacing dichloromethane as deblocking reagent solvent with a less problematic solvent while preserving product yield and quality.[3b]

After solid phase synthesis is complete the phosphorothioate oligonucleotide is cleaved from the solid support and the backbone and bases are deprotected with aqueous ammonia at elevated temperature in sealed containers (55 °C, *ca.* 12 h). Repeatedly heating pressurized glass vessels containing conc. ammonia may potentially lead to vessel failure, and concomitant injury and loss of product. We therefore explored the possibility of performing this step at atmospheric pressure at room temperature in the same otherwise convenient vessels.

We also investigated the mechanical stability of highly crosslinked polystyrene support used in oligonucleotide synthesis, as recycling of re-usable solid supports is an attractive alternative to current single-use supports.[9]

Results and discussion

DMTr-Removal during solid-phase synthesis

In our ongoing efforts to improve the synthesis of oligonucleotides, we wanted to replace dichloromethane with a solvent that is less harmful, recyclable, cheap, and equally efficient for removing DMTr protecting groups. A series of experiments with test sequences on 1 μmol scale indicated that, in contrast to aliphatic solvents (dimethylformamide, hexanes, ethyl acetate, *tert*-butyl methyl ether), aromatic solvents such as benzene, toluene, xylene, chlorobenzene and benzotrifluoride containing DCA (0.36 M) allow rapid and efficient removal of DMTr groups from 5′-*O*-DMTr-protected nucleotides bound to controlled pore glass (CPG) solid support.[3b] Since there was no apparent benefit in using hazardous benzene or chlorobenzene, we compared the performance of toluene, xylenes and benzotrifluoride as solvents for DMTr removal from oligonucleotides bound to a polystyrene-based matrix (Primer Support, Amersham Pharmacia Biotech).

Reactor design and solid support are crucially important to successful oligonucleotide synthesis. In contrast to small scale synthesizers (*e.g.* ABI 394 RNA/DNA Synthesizer) which typically use silica-based solid support, medium (0.2–3 mmol) and large-scale synthesis (>10 mmol) is most commonly performed in packed-bed reactors on polystyrene-based solid supports. Phosphorothioate oligodeoxyribonucleotides[10] PS-d(TCCCGC-CTGTGACATGCATT) (**1**), PS-d(TCCGTCATCGCTC-CTCAGGG) (**2**), PS-d(GTTCTCGCTGGTGAGTTTCA) (**3**), PS-d(GCCCAAGCTGGCATCCGTCA) (**4**) were synthesized on an Amersham Pharmacia Biotech OligoPilot II oligonucleotide synthesizer closely resembling the production-scale synthesizer (APB OligoProcess). Primer support (*ca.* 1.7 g, loading 96 μmol g^{-1} dA^{bz}, 91 μmol g^{-1} dG^{ib}, 88 μmol g^{-1} T, from APB) containing the 3′ terminal nucleoside of the sequence to be synthesized was tightly packed in a steel column (volume 6 ml). Details of the synthesis cycle are given in Table 1. Deblock solution (3% dichloroacetic acid/solvent, 50 ml) was passed through the column for 4 min at each deblock step. Conductivity-based or UV-based DMTr yields were obtained when halogenated solvents (dichloromethane or trifluorotoluene) were used. In contrast, UV-based, but not conductivity-based detritylation yield information was available using solvents like toluene or xylene. The relative performance of deblock solutions was judged by

comparing both quantity and quality of oligonucleotide product. Since recycling solvents may become an issue for ton-scale production of oligonucleotides, we collected the deblock solutions after each DMTr removal. A simple distillation allowed us to recover toluene of high purity that was then re-used as deblock solvent in a subsequent synthesis of **4**. For DMTr-on/DMTr-off purification of the crude oligonucleotide, we used a C$_{18}$ reversed phase HPLC method that allowed facile separation of the 5′-*O*-DMTr-on oligonucleotide from capped failure sequences. The total DMTr-on peak was collected without further fractionation.

Results from analysis of **1**–**4** synthesized using different deblock solutions are summarized in Table 2. The crude yields of **1**–**4** were identical (UV, ±2 OD$_{260}$/μmol) as were the full-length contents of crude (±3%) and purified oligonucleotide product (±1.5%), which were determined by capillary gel electrophoresis (CGE). The relative amount of ($n - 1$)-mer formed is a crucial parameter in these experiments since incomplete DMTr removal would lead to increased ($n - 1$)-mer content. The low relative ($n - 1$)-mer content (2.3–5.0%) of the DMTr-on fraction in HPLC-purified oligonucleotide products demonstrates clearly that DMTr removal with DCA in aromatic solvents toluene, xylene or benzotrifluoride is as efficient as it is with DCA in dichloromethane.

Acid exposure time must be minimized to keep formation of depurinated oligonucleotide sequences to a minimum. Electrospray mass spectrometry was used to determine the amount of depurinated species present in the crude oligonucleotide. The ratio of sequences arising from a loss of adenine or guanine to **4** falls in the narrow range of 2.7 ± 0.3% which shows that exposure to the different deblock solutions for the same length of time (4 min) does not change the impurity profile. The phosphodiester content, as determined by ^{31}P NMR spectroscopy, was also within limits typically observed. Considering cost, boiling points (recycling, environmental exposure), and viscosity (potential pressure build-up during large scale synthesis) issues, we found toluene to be the best alternative to dichloromethane for DMTr removal.

Next, we scaled up the synthesis of **4** another 500 fold using 3% DCA in CH$_2$Cl$_2$ or 3% DCA in toluene to 80 mmol scale (OligoProcess). The rate of DMTr-removal from the 5′-oxygen depends upon the nucleotide to which the DMTr group is bound and increases in the order DMTr-T <DMTr-dC^{bz} <DMTr-dA^{bz} <DMTr-dG^{ib}. The amount of deblock solution required also depends on the length of the oligonucleotide bound to the solid support. The more nucleotides are bound to the support the more acid is absorbed increasing the required acid exposure time as the chain length increases. As a consequence, large-scale detritylation is performed best by carefully monitoring the release of DMTr cations (spectrophotometrically or by conductivity) and adjusting the acid exposure time accordingly. Again, we find equivalency of the crude (CGE full length content 71.4% using DCM, 74.1% using toluene) and purified products (96.5% and 96.3%, respectively).

Room temperature deprotection of **4** with ammonium hydroxide

Cleavage of oligonucleotides from solid support and deprotection of cyanoethyl protected phosphorothioate linkages and nucleobases is performed by treatment with conc. aqueous ammonia at elevated temperature (55 °C) in pressurized reaction vessels for *ca.* 12 h. The halflife time for the rate determining deprotection of dG^{ib} under those conditions is *ca.* 0.5 h. The goal of this investigation was to determine the reaction time required for complete removal of the standard protecting groups from the

Table 1 Synthesis parameters of the cycle used on Pharmacia OligoPilot II Synthesizer

Step	Reagent	Volume/ml	t/min
DMTr removal	3% Dichloroacetic acid/solvent	50	4
Coupling	Phosphoramidite (0.2 M), $1H$-tetrazole (0.45 M)	1.6, 5	5
Sulfurization	Phenylacetyl disulfide (0.2 M)[a]	6	2
Capping	Ac_2O/pyridine/acetonitrile, NMI/acetonitrile	1.7, 1.7	0.5

[a] See ref. 11b.

Table 2 Analytical data of phosphorothioate oligonucleotides **1**–**4** synthesized using different deblock solutions[a]

			Crude		HLPC-purified	
PS-oligonucleotide	Deblock solvent	Crude yield [OD/μmol]	Full length content [area-%][b]	PO content[c,d]	Full length content [area-%][b]	Relative $(n-1)$ content [area-%][b]
1	CH_2Cl_2	125	72	0.6	94	2.4
	Toluene	124	69	0.8	95	2.4
	Xylene	125	72	0.5	95	2.4
	Benzotrifluoride	127	69	0.8	93	2.3
2	CH_2Cl_2	123	73	0.5	93	2.9
	Toluene	121	79	0.3	92	3.5
	Xylene	123	79	0.7	92	3.5
	Benzotrifluoride	124	73	0.4	89	3.3
3	CH_2Cl_2	133	73	0.6	92	5.0
	Toluene	129	74	0.7	90	4.5
4	CH_2Cl_2	148	75	0.3	92	4.3
	Toluene	148	73	0.2	92	3.6
	Toluene (rec.)	148	73	0.3	91	4.2

[a] 3% Dichloroacetic acid/deblock solvent. [b] CGE. [c] ^{31}P NMR. [d] Sulfurizing agent for **1**–**3**: $3H$-1,2-benzodithiol-3-one-1,1-diox-ide,[11a] for **4**: phenylacetyl disulfide.[11b]

nucleobases (dA[bz], dC[bz], dG[ib]) of phosphorothioate oligodeoxyribonucleotides with conc. aqueous ammonia at room temperature (20 °C). Performing the ammonia deprotection at ambient temperature reduces the risk of injuries of personnel and loss of product through explosion of defective glass bottles. Solid support (Primer HL 30, Pharmacia) containing the oligonucleotide was suspended in aqueous ammonia at room temperature and agitated with a magnetic stir bar. Aliquots were taken at different time points (1–120 h), immediately diluted with water, frozen and lyophilized. After reconstitution of the oligonucleotide in water, solid support particles were removed by centrifugation. Phosphorothioate oligonucleotide **4** was converted to the corresponding phosphodiester oligonucleotide using a solution of iodine/THF/N-Me-imidazole.[12] Enzyme catalyzed phosphodiester hydrolysis (phosphodiesterase I) and phosphate hydrolysis (alkaline phosphatase) was performed in one step to yield a mixture of nucleosides which was analyzed by reversed phase HPLC. Removal of benzoyl groups from dC[bz] in **4** is fast and complete disappearance of the dC[bz] peak from the HPLC-chromatogram is observed at the 7 h time point. The half-life is estimated to be *ca.* 0.5 h. Removal of benzoyl groups from dA[bz] nucleotides in **4** is slightly slower, and also complete at the 7 h time point. The half-life is estimated to be *ca.* 1 h. Removal of the isobutyryl groups from dG[ib]-nucleotides in **4** is the rate-limiting step. Very small peaks (<0.1%) of dG[ib] are still detected after 74 h. The half-life is estimated to be *ca.* 7–8 h which compares well with the rate of dG[ib] deprotection of dG[ib] nucleoside bound to CPG support.[13] At the 120 h time point no protected nucleosides were detected by HPLC. The analytical data for **4** deprotected at room temperature for 5 d was compared with that of **4** that had

been deprotected for 17 h at 55 °C. As seen from Table 3, analytical data for both products are identical.

Stability of polystyrene support

Separation of solid support and oligonucleotide containing solution after ammonia treatment is typically performed by filtration. On small scale, filtration through a cotton plug in a pasteur pipet works very well for this purpose, on larger scale, filter paper is used. During this investigation, however, we noted, that filtration could not be adequately achieved for reaction mixtures which had been stirred. Instead, centrifugation was used for separation of the support from the supernatant. Electron microscopic analysis of the solid support surface characteristics from the room temperature experiments (shaken for 10 s once a day over a 4-day period) revealed uniform spheres of 30 microns diameter with smooth continuous outer surfaces [Fig. 1(*a*)]. Support collected from the elevated temperature experiments which received no agitation appeared as round 30 micron beads and was unremarkable in appearance from the room temperature experiment support [Fig. 1(*b*)]. The solid support which was subject to gentle agitation (slow wrist shaking motion) for 4 days appeared to have undergone some disintegration of its immediate surfaces and the spheres were fringed with rough surfaces, which appeared as hazy surface irregularities [Fig. 1(*c*)]. Observations of the support which had been exposed to vigorous stirring with a magnetic bar for a period of 4 days indicated that it had undergone complete disintegration and appeared as a flattened amorphous cake [Fig. 1(*d*)] demonstrating the limited mechanical stability of this highly crosslinked polystyrene polymer. Gentle agitation

Table 3 Deprotection of phosphorothioate **4** with aqueous ammonia at different temperatures

	55 °C, 17 h	20 °C, 5 d	Method
Yield [OD_{260}/μmol]	148	149	UV
Full length, ($n-1$)-mer of crude (%)	73, 4.7	73, 4.8	CGE
Full length, ($n-1$)-mer of purif. (%)	92, 3.4	92, 3.4	CGE
PO-content (%)	5.3	5.3	LC/MS
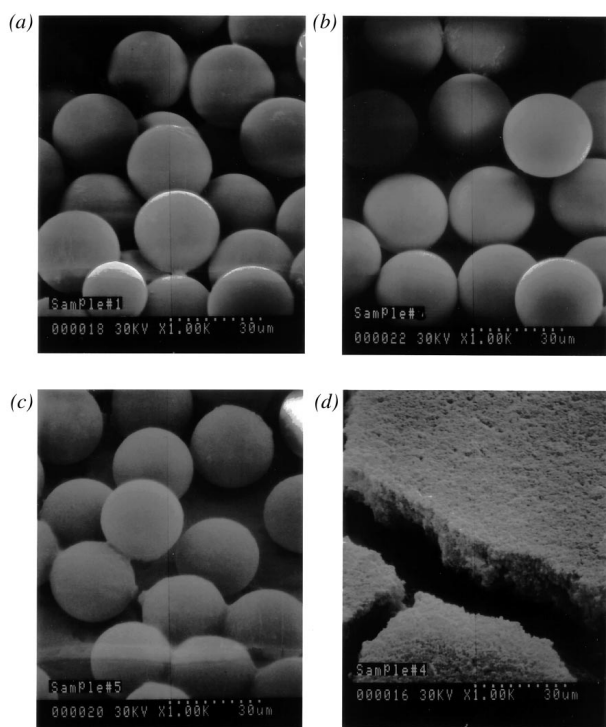
Fig. 1 SEM photographs of Primer Support after cleavage of the oligonucleotide with aqueous ammonia under different conditions. (*a*) Heating for 17 h at 55 °C results in spherical beads with smooth surfaces. (*b*) Minimum agitation once a day for 4 days at room temperature results in spherical beads with smooth surfaces. (*c*) Continuous shaking for 4 days at room temperature leads to fringed beads with rough surfaces. (*d*) Vigorously stirring with a magnetic bar for 4 days at room temperature leads to complete disintegration of the polymer beads.

once a day over the 5 day period allows complete recovery of the oligonucleotide using a simple filtration procedure.

Conclusion

As is evident from the data presented in this paper, a solution of dichloroacetic acid in toluene allows removal of 4,4′-dimethoxytrityl groups from support-bound oligonucleotides to give antisense oligonucleotides **1**–**4** in high yield and purity. Multiple analytical methods showed equivalence to oligonucleotides synthesized with the standard solution of dichloroacetic acid in dichloromethane. In conclusion, we have shown that health-hazardous dichloromethane can be replaced as solvent for deblocking in solid phase synthesis by toluene, without compromising yield or quality of oligonucleotide products. Room temperature deprotection with aqueous ammonia at atmospheric pressure for 5 days reduces the risk that heated and pressurized glass containers pose. Minimum agitation permits separation of polystyrene solid support and oligonucleotide solution by simple filtration.

Experimental

5′-*O*-Dimethoxytrityl-3′-*N,N*-diisopropylamino-*O*-(2-cyanoethyl) phosphoramidites (T, dA^bz, dC^bz, dG^ib) (APB), Primer Support HL (APB), 1*H*-tetrazole (American International Chemical, Natick), phenylacetyl disulfide (Schweizerhall), acetonitrile anhydr. (J. T. Baker) and toluene (Gallade) were used as received. ^{31}P NMR spectra were recorded on a Unity-400 spectrometer (Varian) operating at 161.9 MHz. Capillary gel electrophoresis was performed on a eCAP ssDNA 100 Gel Capillary (47 cm) on a P/ACE System 5000 using tris/borate/7 M urea buffer (all Beckman), running voltage 14.1 kV, 40 °C. Analysis and purification of oligonucleotides by reversed-phase high performance liquid chromatography (RP-HPLC) was performed on a Waters NovaPak C_{18} column (3.9 × 300 mm) using a Waters HPLC system (600E System Controller, 996 Photodiode Array Detector, 717 Autosampler). For analysis an acetonitrile (A)/0.1 M triethylammonium acetate gradient was used: 5% to 35% A from 0 to 10 min, then 35% to 40% A from 10 to 20 min, then 40% to 95% A from 20 to 25 min, flow rate = 1.0 ml min^{-1}; for DMTr-on/DMTr-off purification: 5% to 27% A from 0 to 1 min, 27% A from 1 to 8 min, 27% to 50% A from 8 to 9 min, 9 to 26 min at 50%, flow rate = 1.0 ml min^{-1}, t_R(DMTr-off) 10–11 min, t_R(DMTr-on) 14–16 min. Surface morphology of solid support was examined using a Hitachi S-520 scanning electron microscope. Samples were gently transferred with a spatula to an aluminium specimen stub, mounted with a carbon filled acrylic glue and coated under high vacuum (0.05 mTorr) with a 10 nm layer of gold–palladium. All samples were scanned at 20 kV, and their photographs taken at magnification 1000.

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Development of clean technology

for the production of triols

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Summary

An alternative clean production technology was developed for the synthesis of two triols, trimethylolpropane (2,2-di(hydroxymethyl)butan-1-ol) and trimethylolethane (2,2-di(hydroxymethyl)propan-1-ol) starting from formaldehyde, propionaldehyde and butyraldehyde; the technology is based on the use of solid heterogeneous catalysts in the key process steps, aldolization and aldol hydrogenation. Catalyst screening and kinetic experiments with propionaldehyde and butyraldehyde showed that the desired aldols can be obtained with a high yield and selectivity when anion exchangers with amine groups are used as heterogeneous catalysts and the reaction is carried out in aqueous environment. Suitable reaction temperatures are 50–80 °C with formaldehyde : propion- or butyr-aldehyde ranging from 3 : 1 to 4 : 1. In the second process step, the excess of formaldehyde was separated from the reaction mixture with atmospheric distillation in the presence of excess of water. Catalyst screening and kinetic experiments showed that nickel–chromium and copper–chromium are the most suitable catalysts for the aldol hydrogenation. The experiments carried out at 50–80 °C and 40–80 bar hydrogen gave 100% yields of trimethylolpropane and trimethylolethane. A process scheme for the continuous production of trimethylolpropane and trimethylolethane was proposed.
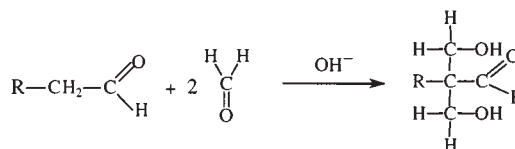
Introduction

Diols and triols are key intermediates in the industrial production of lubricants, surface coatings and synthetic resins. The classical pathway in the diol synthesis is based on the use of alkali-catalyzed aldolization followed by the Cannizzaro reaction.[1] Equimolar amounts of sodium formate ions (*i.e.* formic acid) are formed in the traditional reaction route. This is a serious drawback since formate is an environmentally unfriendly compound, which has to be separated from the product mixture. Appearance of formate as a co-product has also an economically negative impact: the producer of diols and triols is forced to deal with a component which has a low market value. There exists a more efficient production technology for formic acid, namely the synthesis through the Leonard process starting from methanol and carbon monoxide.

An alternative synthesis route for diols and triols based on the utilization of heterogeneous catalysts is thus highly desirable. A long time ago it was discovered that it is possible to stop the reaction at the aldol stage by using the mild bases such as tertiary amines as catalysts instead of NaOH.[2] The carbonyl group of the prepared aldol can be hydrogenated to diol or triol. The co-products are avoided as illustrated by the reaction scheme in Fig. 1.

According to recent literature[3] the process based on heterogeneous catalysis is feasible when formaldehyde and isobutyralde-

New route: heterogeneous catalytic reactions

Aldol condensation
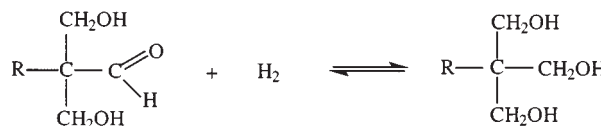
Diol hydrogenation (formation of triol)

Fig. 1 The reaction scheme of the alternative production route.

hyde are used as starting molecules. In case of linear aldehydes, elimination takes place as a side reaction in the presence of weak bases. The elimination gives an unsaturated aldehyde, in case of propion- and butyr-aldehyde methyl- and ethyl-acrolein are obtained. This might be the reason for the laconic and discouraging comment written[3] "numerous attempts to find new routes without HCOOH coproduct have all been unsuccessful".

Green Context

This article describes new cleaner synthesis routes to triols which are important intermediates in the manufacture of many lubricants, surface coatings and synthetic resins. Traditionally these compounds are made by routes which employ alkali and generate large volumes of toxic formate as a co-product. In this new approach both of the key process steps are effectively catalysed using heterogeneous catalysts thus reducing the need for a neutralisation stage (leading to salt waste) and maximising the use of the catalysts. The new routes avoid side-product formation and give the desired products with high yield and selectivity. *JHC*

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Here we report how the dilemma with side products can be surmounted by the selection of proper heterogeneous catalysts and reaction conditions: the desired diols 2,2-di(hydroxymethyl)butanol (trimethylolpropane aldol) and 3-hydroxy-2-hydroxymethyl-2-methylpropanal (trimethylolethane aldol) can be prepared with high yield and selectivity starting from formaldehyde, butyraldehyde and propionaldehyde.

Experimental

Procedure for aldolization experiments

Batchwise aldolization experiments were carried out in a 1.0 dm^3 jacketed glass reactor. Formaldehyde, either as a freshly prepared aqueous solution of paraformaldehyde or as formalin, and *n*-butyraldehyde, propionaldehyde, the commercial weakly basic ion exchange resin catalyst and the solvents, water and methanol, were loaded into the reactor at room temperature. The amount of catalyst used was 160 g, and the total liquid mass was about 800 g. Thereafter, the reactor was heated until the reaction temperature was attained (40–80 °C). The reactor was equipped with a heating jacket and a cooling condenser. The experiments were carried out under nitrogen atmosphere. The first sample was taken at room temperature before switching on the heating system of the reactor. The reaction temperature was reached within 15–20 minutes. The kinetic experiments were carried out with formaldehyde : propion- or butyr-aldehyde ratios of 2 : 1, 3 : 1, 4 : 1 and 8 : 1 at 40–80 °C.

Procedure for formaldehyde separation

Since the aldol solution typically contains >10 wt% formaldehyde, which is known to be a catalyst poison, most of it had to be removed before the catalytic hydrogenation. A suitable formaldehyde separation process for this purpose is steam distillation, which can be carried out in two ways. The classical method is to pass steam into the liquid in the distillation flask, which is heated.[4]

A straightforward way to carry out steam distillation is simply to put a mixture of the organic compound and water in a distillation pot, and carry out an ordinary distillation. In this work the latter method was chosen because of its simplicity and operability in laboratory scale.

The separation of formaldehyde was performed under atmospheric pressure and at 100 °C using a batch volume of 400 ml (200 ml of aldolization product mixed with 200 ml of distilled water). As the first distilled droplets from the condenser were observed, the addition of extra water was commenced. The water feeding was adjusted in order to maintain a constant liquid volume in the distillation flask. Reducing the formaldehyde content under 1 wt% required an addition of 750 ml water into the distillation pot. The average distillation time was 3 h. After the distillation, 200 ml water was evaporated from the solution with a rotary evaporator to remove the water which was added before the distillation.

Procedure for hydrogenation experiments

The experiments were performed in a pressurized autoclave (1 dm^3) to which a degasing unit was connected. The pressure, the temperature and the agitation velocity were controlled and registered during the experiment.

The supported Ni catalyst (5 g) was placed into the reactor and the pressure was regulated to 2 bar and the gas flow to 500 ml min^{-1}. The desired temperature (400 °C) was achieved with a temperature controller, after which the hydrogen flow was increased to 750 ml min^{-1} and the catalyst was activated for 1 h. After the activation, the gas flow was maintained constant and the reactor was cooled down.

A hydrogenation mixture was prepared by stirring 150 ml formaldehyde separated aldol solution into 150 ml methanol. The hydrogenation mixture was poured into the bubbling unit where it was saturated with hydrogen during 10–15 min in order to remove dissolved oxygen from the solution. The reactor pressure was reduced from 2 to 1.5 bar, whereas the pressure in the bubbling unit was increased to 8 bar. The solution was injected into the reactor and data acquisition was switched on. When the temperature was 15–20 °C below the desired one, the agitation was adjusted to 1000 rpm.

Chemical analyses

The analyses were carried out with a High Performance Liquid Chromatograph equipped with a LiChrosorb RP-18 column (5 μm, 250 × 4 mm) and diode array (DA) and refractive index (RI) detectors. Two separate methods were applied to analyse the compounds: a derivatization method was used for the quantitative determination of aldehydes, aldols and unsaturated aldehydes, while a straightforward method was developed for measuring the contents of triols and organic acids.

In the derivatization method, 2,4-dinitrophenylhydrazine was used as a reagent in acetonitrile solution.[5] The carbonyl compounds react with acidified DNPH in the liquid phase, forming the corresponding hydrazones, which were easily separated by liquid chromatography and detected with the DA detector at a wavelength of 360 nm, where the absorption maximum for hydrazones is located.[5] The components were separated by gradient elution, with 4 vol% ACN in deionized water (MILLI-Q^{TM}) and pure ACN as eluents (flow: 1 ml min^{-1}). The column temperature was 40 °C.

Triols and acids were separated by isocratic elution. Acids were detected with the DA detector at the wavelength of 210 nm and triols with the RI detector. The temperature in the column was 40 °C.

Results and discussion

Aldolization

Preliminary experiments with triethylamine showed that it is possible to stop the aldolization reaction as illustrated in Fig. 2. No Cannizzaro reaction was observed.
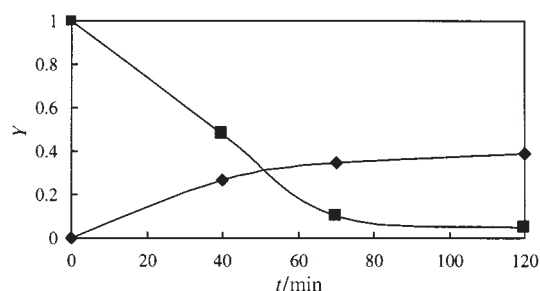

Fig. 2 Aldolization experiment in the presence of 10% triethylamine. *Conditions*: 80 °C, formaldehyde : butyraldehyde 2 : 1. ■ = butyraldehyde; ◆ = aldol.

However, the use of heterogeneous catalysts is more attractive since the catalyst separation problem is avoided. Thus the research was oriented towards the replacement of triethylamine with heterogeneous catalysts. Anion exchange resins with amine groups can catalyze aldolization. The first experiments with propionaldehyde and butyraldehyde were carried out in methanol–water. The results were promising but considerable amounts of acrolein were formed as by-product as demonstrated in Fig. 3. Typically, the final molar ratio between the desired aldol and alkylacrolein was approximately 2:1. Furthermore, propionaldehyde and butyraldehyde underwent acetalization with the solvent methanol: the acetalization was
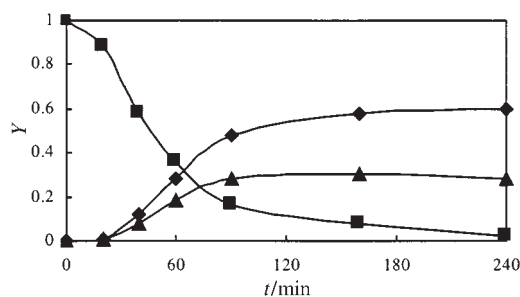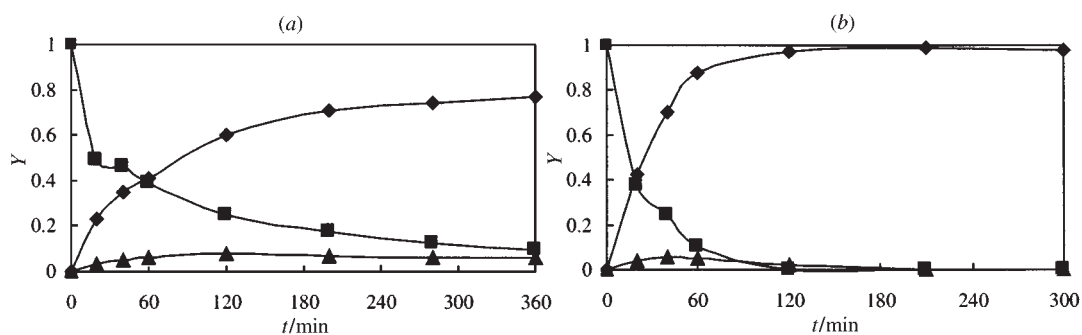
Fig. 3 Aldolization of butyraldehyde at 80 °C in methanolic solvent with formaldehyde:butyraldehyde 8:1 in the presence of an anion exchange resin. ■ = butyraldehyde; ▲ = Ethylacrolein; ◆ = aldol. Catalyst E (see Table 1).
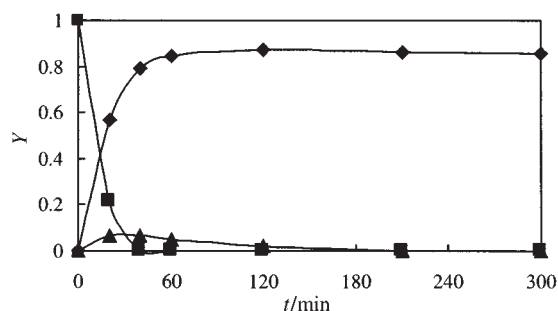
Fig. 4 Aldolization of propionaldehyde at 70 °C in aqueous solvent with formaldehyde:propionaldehyde = 4:1. ■ = propionaldehyde; ▲ = methylacrolein; ◆ = aldol. Catalyst E (see Table 1).
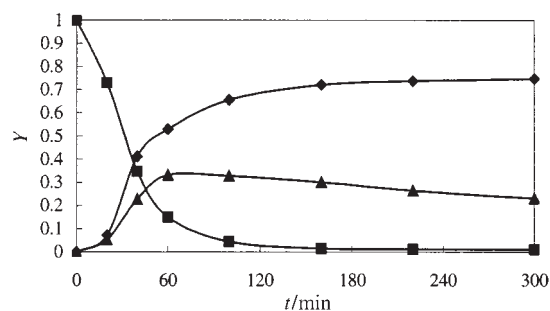
Fig. 5 Aldolization of butyraldehyde at 70 °C in aqueous solvent with formaldehyde:butyraldehyde = 4:1. ■ = butyraldehyde; ▲ = ethylacrolein; ◆ = aldol. Catalyst E (see Table 1).

confirmed with NMR spectroscopy.[6] Acetalization is a harmful reaction in this context, since it destroys the reagent.

The change of the methanol–water mixture to pure water was the breakthrough in the process development: the acetalization was suppressed and a clearly more favourable product distribution was obtained. Examples of the aldolization of propionaldehyde and butyraldehyde are provided in Figs. 4 and 5, respectively.

Excess formaldehyde favoured the formation of the aldols as expected on the basis of kinetics. The effect of formaldehyde on the product distribution is illustrated in Figs. 6 and 7. In best cases, we could obtain almost 100% selectivity to aldol [Fig. 6(*b*)].

Several commercial weakly basic ion-exchange resins with tertiary amines as functional groups were investigated. The best selectivities with respect to aldol were obtained with the catalysts A and B (Table 1). For these catalysts, the aldol selectivity typically exceeded 85%.

At the initial and intermediate stages of the reaction, the product distribution followed a parallel pattern as demonstrated in Figs. 8 and 9, but later on, the yield of the aldol increased more rapidly than that of the alkylacrolein. The reason is the back-conversion of the alkylacrolein to the first aldol, which is aldolized further to the desired product. This feature is very favourable from the practical point of view: the product distribution can be improved by allowing the reaction to continue.
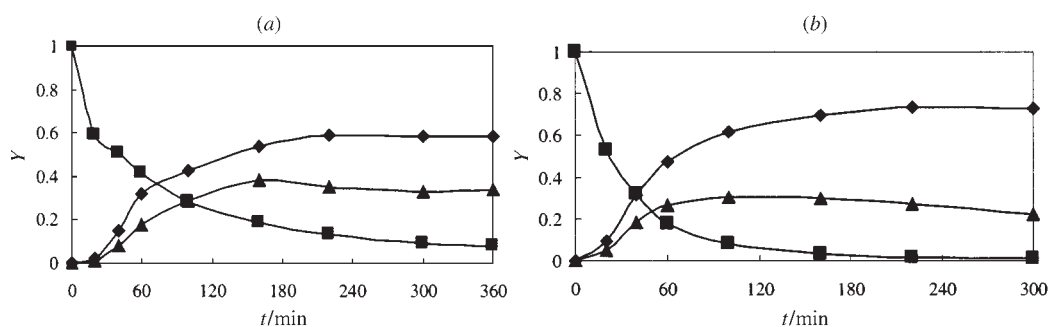
Formaldehyde separation

The last step of the process, the aldol hydrogenation, is in principle more straightforward, since no selectivity problems appear. The challenge is to improve the reactivity of the bulky aldol molecule and to avoid catalyst poisoning by formaldehyde. Since formaldehyde is known to have a deteriorating effect on typical hydrogenation catalyst metals such as nickel, it should be separated from the reaction mixture after the aldolization step. Distillation of formaldehyde directly from the product mixture is not a viable option since also large amounts of water are distilled away, and the formaldehyde concentration increases resulting to oligomerization. To maintain a low enough formaldehyde concentration in the liquid phase, water was continuously added to the distillation pot during the process. In this way it was possible to easily reach low formaldehyde contents, less than 0.5 wt%.

Aldol hydrogenation

The aldol hydrogenation in a low formaldehyde mixture is straightforward. Several catalysts were screened, some examples are provided in Table 2.

The most active catalysts turned out to be nickel–chromium and copper–chromium alloys. A complete conversion and selectivity were achieved with these catalysts. When formaldehyde was present in the reaction mixture, a shoulder was observed in
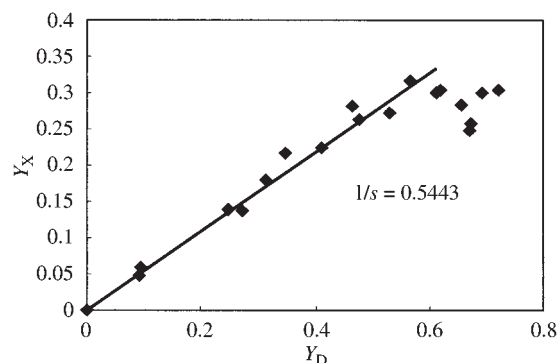

Fig. 6 Aldolization of propionaldehyde with formaldehyde:propionaldehyde = 2:1 (*a*) and 8:1 (*b*) in aqueous solvent at 40 °C. ■ = propionaldehyde; ▲ = methylacrolein; ◆ = aldol. Catalyst E (see Table 1).

Fig. 7   Aldolization of butyraldehyde with formaldehyde : butyraldehyde = 2 : 1 (*a*) and 4 : 1 (*b*) in aqueous solvent at 60 °C.
■ = butyraldehyde; ▲ = ethylacrolein; ◆ = aldol. Catalyst E (see Table 1).

Table 1   Aldol and ethylacrolein yields and molar ratio between the main products after 7 h aldolization of butyraldehyde on different weakly basic ion exchange resins

Resin	Matrix	Type	Yield of aldol (%)	Yield of ethylacrolein (%)	Aldol : Ethylacrolein
A	Acrylic/DVB	macro	85.2	13.1	6.5
B	Acrylic/DVB	gel	85.2	14.7	5.8
C	Polystyrene/DVB	macro	84.2	15.8	5.3
D	Acrylic/DVB	gel	80.8	19.1	4.2
E	Acrylic/DVB	gel	77.6	22.4	3.5
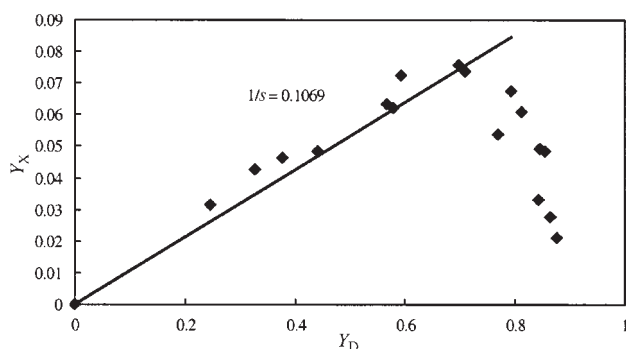
Fig. 8   The concentration of methylacrolein *vs.* the concentration of aldol in the aldolization of propionaldehyde. *Conditions*: formaldehyde-:-propionaldehyde = 4 : 1; 40–70 °C; aqueous solvent. Y_X = amount of methylacrolein : initial amount of propionaldehyde (in mol); Y_D = amount of aldol : initial amount of propionaldehyde (in mol).
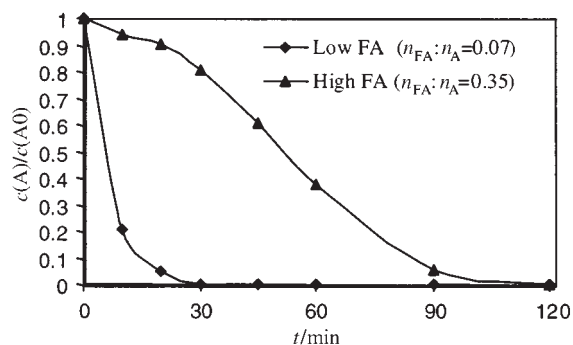
Table 2   Screened hydrogenation catalysts according to primary metals

Nickel	Copper	Noble metals
Ni–Cr/SiO$_2$	Cu–Zn/Al$_2$O$_3$	Ru–Pd/C
Ni/Al$_2$O$_3$	Cu–Cr/Cr$_2$O$_3$	Ru/C
		Pt–Pd/C
		Pt/C

the kinetic curves of the aldol (Fig. 10). The reason might be oligomerization of the formaldehyde on the catalyst surface that prevents the hydrogenation of the aldol. After completing the hydrogenation of formaldehyde, the hydrogenation of the aldol accelerated. However, by a further suppression of the formaldehyde content of the starting mixture, the hydrogenation velocity was considerably enhanced as demonstrated in Fig. 10.

Fig. 9   The concentration of ethylacrolein *vs* the concentration of aldol in the aldolization of butyraldehyde. *Conditions*: formaldehyde : butyraldehyde = 4 : 1; 50–70 °C; aqueous solvent. Y_X = amount of methylacrolein : initial amount of propionaldehyde (in mol); Y_D = amount of aldol : initial amount of propionaldehyde (in mol).

Fig. 10   The effect of formaldehyde concentration on the hydrogenation of aldol at 90 °C and 70 bar.
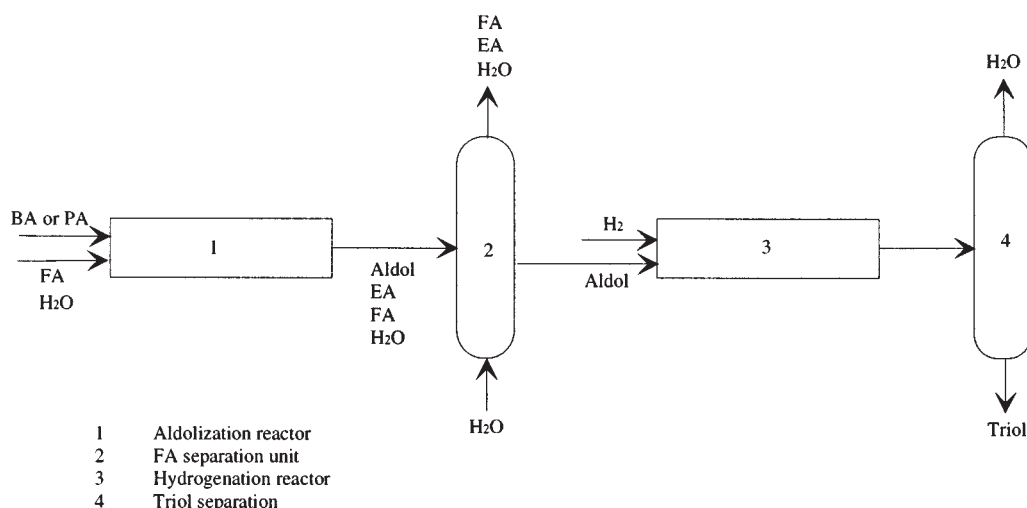
Fig. 11 Flowsheet for the continuous process.

Conclusions

A new and clean three-step production technology was developed for the synthesis of two triols, trimethylolpropane and trimethylolethane. The new technology is based on three steps: aldolization of the reagent aldehydes over anion exchange resins, formaldehyde separation and aldol hydrogenation over nickel–chromium catalysts. A principal flowsheet for a continuous process is sketched in Fig. 11.

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Mg-Al-O-But–Hydrotalcite:

a mild and ecofriendly catalyst for the cyanoethylation of alcohols and thiols†

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Summary

Mg-Al-O-But–Hydrotalcite is found to be a mild and efficient catalyst for the cyanoethylation of alcohols and thiols in quantitative yields. Exclusive synthesis of 3-alkoxypropionitriles or 3-alkylmercaptopropionitriles is realised by compatible basic sites of Mg-Al-O-But–hydrotalcite. The present ecofriendly catalytic system is a potential alternative to soluble bases.

Introduction

Stringent environment protection laws, public and corporate pressure to reduce the amount of toxic waste and by-products arising from the chemical processes have prompted the development of innovative and environment-friendly new technologies[1] by solid acid–base catalysts. Therefore, enviro-economics has become the focused theme for the development of new processes for existing products and new products.[2] The use of heterogeneous catalysts has made significant advancement in the development of new methodologies in organic synthesis targeted to dispense the conventional and waste generating reagents and achieve high atom economy to be applied in the fine chemical sector.[3]

Cyanoethylation is one of the important reactions for the synthesis of drug intermediates, plasticizers, insecticides, emulsifiers, additives for synthetic rubber and physiologically active compounds.[4] Acrylonitriles undergo cyanoethylation with compounds containing an active hydrogen to form β-alkoxynitriles which are in turn converted to carboxylic acids by hydrolysis or to amines by reduction. Generally cyanoethylation proceeds in the presence of soluble base catalysts[4,5] such as alkali hydroxides,[6] alkali alkoxides,[7] tetraalkylammonium hydroxides,[7] alkali metal or tetraalkylammonium salts of partial phosphate esters, alkyl mercaptans, cresols, and partial pyrophosphate esters.[8] However, these catalysts need to be neutralised before purification of the product, thus resulting in the generation of waste, loss of catalyst and reduced product yields. Heterogeneous anion exchange resin catalysts are also used for this reaction[9–11] but the resins become inactive after a few runs possibly due to the formation of a film of polyacrylonitrile on the surface of the resin. Recently, Hattori and Kabashima[12,13] have reported the use of alkaline metal oxides, carbonates, hydroxides and alumina supported KF and potassium hydroxide catalysts and found MgO to be very active for cyanoethylation of alcohols. The calcination protocol seems to play a key role in evolving a very active MgO catalyst. Various fluorides supported on basic alumina, MgO, CaO, BaO, silica gel, or Celite are explored[14] in the cyanoethylation of polytetrahydrofuran (hydroxy number 169) and cesium

and potassium fluorides supported on basic material have effected the reaction.

Solid bases in the form of layered double hydroxides (LDHs) or hydrotalcite like compounds (HTLCs) are used extensively as adsorbents, anion exchangers and most importantly as basic catalysts.[15] Earlier, we had designed and developed Mg-Al-O-But–hydrotalcite by incorporation of *tert*-butoxide by an exchange process to tune up the hydrotalcites for higher basicity and found them to be excellent catalysts for aldol condensations[16] and the epoxidation of olefins.[17]

Results and discussion

Here we describe cyanoethylation of alcohols and thiols catalysed by Mg-Al-O-But–hydrotalcite affording high yields and selectivities. This is the first report on the cyanoethylation of thiols catalysed by solid base catalysts.

The general reaction scheme for the cyanoethylation is shown in Scheme 1. The reaction of acrylonitrile with alcohols or thiols
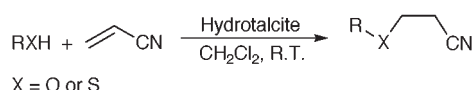
Scheme 1

is fast and forms the addition product generally in high conversion and yield. The catalyst was found to be highly active for alcohols and thiols. The selectivity for the corresponding 3-alkoxypropionitriles and 3-alkylmercaptopropionitriles was quantitative (Table 1). It is interesting to note that the 3-alkylmer-

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> **Green Context**
>
> Cyanoethylation is a widely used reaction in organic chemistry with areas of application including pharmaceutical intermediates, emulsifiers, plasticizers and additives for synthetic rubber. Traditionally the reaction is carried out in the presence of soluble bases such as metal hydroxides but an aqueous quench step is employed to separate the resulting organic products leading to the destruction of the base (by subsequent neutralisation) and the production of an aqueous salt waste stream. Previous attempts to use solid bases in this reaction have had limited success but in this article a high-yielding very selective procedure for the cyanoethylation of alcohols and thiols based on a basic hydrotalcite is described. This environmentally friendly procedure leads to minimal waste and gives high process efficiency.   *JHC*

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† IICT communication no. 4405.

Table 1 Cyanoethylation catalysed by Mg-Al-O-Bu^t–hydrotalcite

Entry	Alcohol or thiol	t/h	Product	Yield^a (%)
1	MeOH	0.6	MeO–CN	92^b
2	EtOH	1.5	EtO–CN	96^b
3	Me$_2$CHOH	4.0	Me$_2$CHO–CN	90^b
4	Ph—CH$_2$OH	1.5	Ph—CH$_2$O–CN	100
5	Me—CH$_2$CH$_2$CH$_2$OH	2.0	Me—O–CN	100
6	CH$_2$=CH—CH$_2$OH	4.0	CH$_2$O–CN	87
7	CH$_2$OH (allylic)	2.5	CH$_2$O–CN	89
8	Ph—CH$_2$OH (cinnamyl)	2.0	Ph—CH$_2$O–CN	80
9	OH (pentanol)	3.0	O–CN	100
10	HOH$_2$C–C(NH$_2$)(Me)–CH$_2$OH	2.0	NC–OH$_2$C–C(NH$_2$)(Me)–CH$_2$O–CN	98
11	SH (butyl)	0.5	S–CN	90
12	SH (hexyl)	0.6	S–CN	100
13	cyclohexyl SH	1.5	cyclohexyl S–CN	90
14	Me—[CH$_2$]$_{11}$—SH	0.5	Me—[CH$_2$]$_{11}$—S–CN	94

^{a} Yields based on ^{1}H NMR. ^{b} Isolated yields.

captopropionitriles, valuable intermediates for dyes, drugs and insecticides,[18] are realised by employing solid bases. However, the catalyst is inert for the cyanoethylation of amines, and utilising this opportunity we have successfully prepared alkoxynitriles bearing amino groups for the first time (entry 10).

We compared the activity of the Mg-Al-O-Bu^t–hydrotalcite catalyst to a variety of soluble and solid bases such as metal oxides, γ-alumina,[12] KF–alumina,[12] KOH–alumina,[13] hydrotalcites[19] and rehydrated Mg-Al–hydrotalcite[19] in the cyanoethylation reaction of acrylonitrile with methanol as a model reaction in order to demonstrate the efficacy of our catalyst (Table 2). Although the reaction of acrylonitrile with methanol using basic alkali earth metal oxides as catalysts afforded good yields, these

catalysts require longer reaction times and high temperature. There is no cyanoethylation reaction with γ-alumina, but the catalysts, KF, KOH doped on alumina gave moderate to good yields. The samples of hydrotalcites as synthesised and calcined showed poor activity. On rehydration, Mg-Al–hydrotalcite offers excellent yields. The present modified hydrotalcite developed through the exchange of Bu^{t}O displayed superior activity, two to ten times that over the reported hydrotalcites, basic oxides, and potassium fluoride and hydroxide doped catalysts.

A plausible mechanism for the cyanoethylation of alcohols with acrylonitrile is illustrated in Scheme 2. The incorporated *tert*-butoxide of the hydrotalcite reacts with alcohol to form the respective alkoxide on the basic sites of the catalyst. The alkox-

Table 2 Cyanoethylation reaction between acrylonitrile with methanol using various base catalysts.[a]

Entry	Catalyst	t/min	Conversion(%)[b]	Specific activity/ mmol g^{-1} h^{-1}[d]
1	Mg-Al-O-Bu^t–hydrotalcite	40	92[c]	110.4
2	γ-Alumina	120	0	0
3	KF/Alumina	120	52.3	10.5
4	KOH/Alumina	120	85.3	17.1
5	MgO	120	98.7	19.7
6	CaO	120	94.7	18.9
7	BaO	120	78.2	15.6
8	Rehydrated Mg-Al hydrotalcite	45	99.8	53.2
9	Hydrotalcite (uncalcined)	120	2.5	0.5
10	Hydrotalcite (calcined)	120	20	4.0

[a] Reaction temp., 323 K, catalyst 0.100 g, unless otherwise stated. [b] Conversion was calculated by the decrease in acrylonitrile percentage. [c] Reaction temp., room temp. using 0.050 g catalyst, isolated yield.[d] Specific activity = mmol of 3-methoxypropionitriles obtained per gram of catalyst per hour.
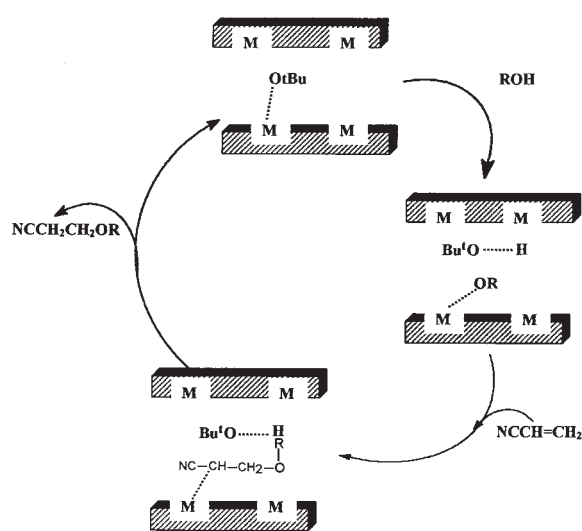
Scheme 2

ide anion is stabilised with the surface metal cationic charge and further reacts with acrylonitrile to form the 3-alkoxypropanenitrile anion, which on interaction with alcohol yields 3-alkoxypropanenitrile.

The present Mg-Al-O-Bu^t–hydrotalcite catalyst is much more active than hydrotalcites and rehydrated hydrotalcite in cyanoethylation reactions. The process of hydration generates hydroxy groups in the interlayers of hydrated hydrotalcites.[19] Understandably, the Bu^{t}O anion incorporated hydrotalcite is more basic than the hydrated hydrotalcite and facilitated easy formation of alkoxide in the hydrotalcite discussed in the mechanism.

An attempt was made to check the reusability of the catalyst in the following manner. The substrates, catalyst and solvent were taken and the reaction was performed as usual for the specified time. Then stirring was stopped and the reaction mixture was withdrawn with a syringe. Fresh substrate and solvent were added to the residual catalyst and the reaction performed in the usual manner. The activity of the catalyst was found to be the same.

In the cyanoethylation reaction catalysed by soluble base (NaOH),[5] each tonne of the substrate requires 50 kg of the base (calculated based on 5 wt% of the base, NaOH employed in the reaction) which has to be neutralised with an acid to generate 72

kg of total dissolved salt (NaCl). The organic waste generated depends upon conversion and selectivity of the specific reaction. The present catalyst can be recycled several times, if proper care is taken. Assuming that our catalyst lasts for 20 recycles, 5–6 kg catalyst per tonne of product has to be disposed as solid waste. Since selectivity is very high, there is no substantial amount of organic waste to be disposed of.

Thus, compatible basic sites present in the Mg-Al-O-Bu^t–hydrotalcite can promote the cyanoethylation reaction with excellent yields in shorter times. The advantages are high catalytic activity under very mild liquid phase conditions, easy separation of the catalyst by simple filtration, excellent yields and 100% selectivity of 3-alkoxypropionitriles at faster rates of reaction, involvement of non-toxic and inexpensive materials, and zero emission of pollutants. The present catalytic system is a potential alternative to soluble bases.

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20 *Representative procedure*: a 100 ml two-necked round bottomed flask was charged with Mg-Al-O-Bu^t–HT (0.05 g) and acrylonitrile (4 mmol) in dry CH_2Cl_2 under nitrogen atmosphere. Alcohols or thiols (4 mmol) were then added to the reaction mixture which was then stirred at room temperature and monitored by TLC. After completion, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The product was analysed by ^{1}H NMR and mass spectrometry.

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