Green chemistry in developing countries

Several years ago I lectured at an international education conference to an audience of schoolteachers from all over the globe, including underdeveloped and developing countries. The subject of my lecture was clean technology and the increasing legislative pressure on chemical companies in European and other developed countries to “clean up their act”. I extended the discussion to the view that such companies would find it increasingly difficult to simply move their environmentally unacceptable manufacturing to other countries. I was subsequently challenged by members of the audience who pointed out that taking on such manufacturing, and indeed dealing with the waste from inefficient chemical processes, could be very important to the economies of less wealthy nations. It was a sobering reminder of the heterogeneity of wealth in the world and a realisation that priorities can be very different in different regions. Nonetheless, we can no longer assume that out-dated wasteful processes will be accepted in developing countries, or indeed that it is considered acceptable for a first-world country to try to take advantage of less rigorous local regulations and relocate hazardous or high-waste manufacturing. As more and more chemical manufacturing moves to developing countries it is very important that the established chemistry communities in Europe and America work with their new chemical cousins to help to introduce the principles of green chemistry in order that past mistakes are not repeated.

In the light of this it is particularly pleasing to see the first major green chemistry conference in India, which is to be held in Delhi in January 2001. The IUPAC International Symposium on Green Chemistry will bring together a range of topics in green chemistry and related environmental topics. These include biocatalysis, the chemistry of energy production, fresh water ecosystems, the elimination of greenhouse gases and eco-friendly chemical technologies. The advisory panel for the event has excellent international representation from North and South America, Europe, Asia and Australasia. It is very appropriate that apart from the “usual suspects” the nations represented include some of those less commonly seen at major green chemistry events such as Estonia and Argentina. We wish them every success with this important event and hope that it encourages others to consider organising green chemistry events in their corner of this ever-smaller world.

Of course the green chemistry message still needs substantial dissemination in the first world countries where education and industry are beginning to respond though much remains to be done. With this in mind the first Royal Society of Chemistry International Conference on “Green Chemistry: Sustainable Products and Processes” will be held in Swansea, UK, in April 2001. This is the first major conference to be held in association with the Green Chemistry Network. This conference will cover developments at the frontiers of chemistry and chemical engineering and will include a session on education and promotion, and will feature presentations from the winners of the first UK Green Chemistry awards. The awards follow in the footsteps of the highly successful US Presidential Green Chemistry Challenge Awards, the latest round of which are featured in an article in this issue. As with the conferences we hope that new awards schemes will encourage a better understanding and appreciation of the importance of green chemistry throughout the world.

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Advances in green chemistry recognized in the United States

Tracy C. Williamson and Mary Kirchhoff of the Office of Pollution Prevention and Toxics, at the U.S. EPA and Paul T. Anastas of the White House Office of Science and Technology Policy describe this year's Presidential Green Chemistry Challenge Awards

In the United States, as around the world, green chemistry is changing the way the central science is done, both in the research laboratory as well as in industry. One of the reasons for this broad appeal is the track record of excellence green chemistry has attained in meeting both fundamental scientific challenges as well as economic and industrial challenges, simultaneously. It is to recognize outstanding accomplishments of this type that the Presidential Green Chemistry Challenge Awards were established in 1995.

This year the 2000 Presidential Green Chemistry Challenge Awards once again recognized accomplishments in the five categories of academic, small business, alternative synthetic pathways, alternative reaction conditions and designing safer chemicals. The breadth of innovation in this year's collection of award winners, reinforces the understanding of green chemistry as an approach that can improve the wide array of the uses of chemicals in our daily lives from pharmaceuticals to agriculture to coatings.

The award ceremony at the National Academy of Sciences featured keynote addresses from President Clinton's Science Advisor, Dr. Neal Lane, as well as speeches from Dr. Darryl Busch, President of the American Chemical Society, and Dr. Kenneth Shine, President of the National Institute of Medicine. The five award winners were:

Academic Category

Professor Chi-Huey Wong, The Scripps Research Institute, was selected for his pioneering work on the development of effective enzymes and the design of novel substrates and processes for large-scale organic synthesis. The methods and strategies that Professor Wong developed have made possible synthetic transformations that are otherwise impossible or impractical, especially in the areas vitally important in biology and medicine, and have pointed the way toward new green methodologies for use in large-scale chemistry. A recent study by the Institute for Scientific Information ranked Professor Wong in the top 15 of the most cited chemists in the world for the period 1994 to 1996. According to this study, he is also the most cited chemist worldwide working in the field related to enzymes. Some of the strategies and methods described here are breakthrough achievements that laid the framework for much of the current use of enzymes as catalysts in large-scale organic synthesis.

The techniques and reagents developed in this body of pioneering work have been used widely today for research and development. The scope of contributions ranges from relatively simple enzymatic processes (*e.g.* chiral resolutions and stereoselective syntheses) to complex, multi-step enzymatic reactions (*e.g.* oligosaccharide synthesis). For example, the irreversible enzymatic transesterification reaction using enol esters in environmentally acceptable organic solvents invented by Wong represents the most widely used method for enantioselective transformation of alcohols in pharmaceutical development.

All of these new enzymatic reactions are carried out in environmentally acceptable solvents, under mild reaction conditions, at ambient temperature, and with minimum protection of functional groups. It represents a new field of green chemistry suitable for large-scale synthesis that is impossible or impractical to achieve by non-enzymatic means.

Small Business Category

RevTech, Inc., was selected for developing a method to decorate glass containers that are aesthetically pleasing and durable and can be obtained in a cost-effective, environmentally friendly, and energy efficient manner. In the Envirogluv™ process, inks are cured directly on the glass by exposure to UV radiation. The human health and environmental benefits of the Envirogluv™ process are many compared to traditionally used decorating methods such as paper labels, decals, or applied ceramic labeling. The ink compositions used in the Envirogluv™ process do not contain any heavy metals and contain little to no VOCs. All pigments used are biodegradable. High baking often required in traditional decorating methods therefore is not necessary, thereby providing additional safety and environmental benefits such as reduced energy consumption and reduced change of worker injury. In addition, there is lower raw materials usage and the process does not generate any waste ink.

Furthermore, Envirogluv™ decorated glass containers eliminate the need for extra packaging and are completely recyclable. Applications include tableware, cosmetics containers, and plate glass, just to name a few.

Alternative Synthetic Pathways

Roche Colorado Corporation was selected for developing a new and efficient synthesis of the potent antiviral agent ganciclovir (Cytovene®). This drug is used to treat cytomegalovirus retinitis infections in patients whose immune systems have been compromised, including those with AIDS and patients who are recipients of solid tissue transplants. In the early 1990s, Roche Colorado Corporation developed the first commercially viable process for the production of Cytovene®. By 1993, chemists at RCC's Boulder Technology Center designed a second process for the production of Cytovene®, which at the time, had an estimated commercial demand of approximately 50 metric tonnes per year. Leveraging the basic principles of green chemistry and molecular conservation into the design

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Alternative Synthetic Pathways Award to Roche Colorado Corporation: (left to right) Dr. Daryle H. Busch, President, American Chemical Society; Dr. Neal Lane, Assistant to the President for Science and Technology, The White House; Don Fitzgerald, Director, Legal Affairs and Environmental Health and Safety, Roche Colorado Corporation; Susan H. Wayland, Acting Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

process, significant improvements were demonstrated in the second generation Guanine Triester (GTE).

Compared to the first generation commercial manufacturing process, the GTE Process reduced the number of chemical reagents and intermediates from 22 to 11, increased the product yield by more than 25%, eliminated the (only) two hazardous solid waste streams, eliminated 11 different chemicals from the hazardous liquid waste streams, and, of the 5 ingredients not incorporated into the final product, 4 of the ingredients were efficiently recycled and reused. In summary, the new GTE Process clearly demonstrates the successful implementation of the general principles of green chemistry: the development of environmentally friendly syntheses, including the development of alternative syntheses utilizing non hazardous and non toxic feedstocks, reagents, and solvents; elimination of waste at the source (liquid waste: 1.12 million kg per year and solid waste: 25,300 kg per year); and elimination of the production of toxic wastes and by-products. Roche Colorado's Guanine TriEster Process (GTE) is registered with the FDA as the current manufacturing process for the world's supply of Cytovene® and is generally applicable to the synthesis of other antiviral agents, such as acyclovir (Zorivax®).

Alternative Reaction Conditions

Bayer Corporation was selected for devising two-component (2K) polyurethane coatings that use water as the carrier, replacing solvents that contain volatile organic compounds (VOCs) and hazardous air pollutants (HAPs) found in conventional 2K solventborne polyurethane coatings. Two-component waterborne polyurethane coatings are an obvious solution to the deficiencies of 2K solventborne polyurethanes and aqueous polyurethane dispersions first investigated as substitutes for the solvent-borne systems, but have only recently been commercialized due to the particular chemistry of the reactive components of polyurethane. In order to bring 2K waterborne polyurethane coatings to the US market, new waterborne and water reducible resins had to be developed. To overcome some application difficulties, new mixing/spray equipment was also developed. For the technology to be commercially viable, an undesired reaction of a polyisocyanate crosslinker with water had to be addressed, as well as problems with the chemical and film appearance resultant from this side reaction.

The work done on the 2K waterborne polyurethanes over the past several years has resulted in a technology that will provide several health and environmental benefits. VOCs will be reduced by 50–90% and HAPs by 50–99%. The amount of chemical by-products evolution from films in interior applications will also be reduced, and rugged interior coatings with no solvent smell will now be available. Today, 2K waterborne polyurethane is being applied on industrial lines where good properties and fast cure rates are required for such varied products as metal containers and shelving, sporting equipment, metal and fiberglass reinforced utility poles, agricultural equipment, and paper products. Flooring coatings, wood, automotive, and military applications will also benefit from the 2K waterborne polyurethane technology.

Designing Safer Chemicals

Dow AgroSciences was selected for the development of the Sentricon Termite Colony Elimination System. The annual cost of termite treatments to the US consumer is about $1.5 billion each year and as many as 1.5 million homeowners will experience a termite problem and seek a control option. Inherent problems with the use of traditional chemical barrier approaches for subterranean termite control created a need for a better method.

The search for a baiting alternative was the focus of a research program established by Dr. Nan-Yao Su of the University of Florida who, in the 1980s, had identified the characteristics needed for a successful termite bait toxicant. The unique properties of hexaflumuron made it an excellent choice for use in controlling subterranean termite colonies. The Sentricon* *Termite Colony Elimination System*, developed by Dow AgroSciences in collaboration with Dr. Su, was launched commercially in 1995 after receiving EPA registration as a reduced risk pesticide. Sentricon represents truly novel technology enabling an Integrated Pest Management approach using monitoring and targeted delivery of a highly specific bait. Because it eliminates termite colonies threatening structures using a targeted approach, Sentricon delivers unmatched technical performance, environmental compatibility, and reduced human risk. The properties of hexaflumuron as a termite control agent are attractive from an environmental and human risk perspective; but more importantly, the potential for adverse affects is dramatically reduced since it is present only in very small quantities in stations with termite activity. The comparisons to barrier methods show significant reduction in the use of hazardous materials and substantial reduction in potential impacts on human health and the environment. More than 300,000 structures across the U.S. are now being safeguarded through application of this revolutionary technology and adoption is growing rapidly.

Conclusion

Both the winners and the nominees of the Presidential Green Chemistry Challenge Award provide excellent examples for the scientific and industrial community to emulate in attaining environmental and economic goals simultaneously. Institutions interested in participating in the 2001 Presidential Green Chemistry Challenge Awards can get more information at http://www.epa.gov/greenchemistry.

For further details please contact Tracy Williamson or Mary Kirchhoff at the Office of Pollution Prevention and Toxics, U.S. EPA, Washington D.C., USA. or Paul Anastas at the Executive Office of the President, White House Office of Science and Technology Policy, Washington, D.C., USA.

NEWS

New web sites

- The website of the "Green and Sustainable Chemistry Network, Japan" is now live: http://www.gscn.net/
- The European Foundation for the Improvement of Living and Working Conditions now has a Sustainable Development website: http://susdev.eurofound.ie/

Award for Green Chemistry Network

The RSC Green Chemistry Network has won a prestigious Green Apple Award for promoting Environmental Best Practice. The annual UK Green Apple awards are organised by the Green Organisation, an independent not for profit organisation who receive most of their funding from the Chartered Institute of Environmental Health, EMP Publishing and MJ Municipal. These awards are given to all sections of the community but, historically, a significant number of winners come from district councils and local authorities. All together over 400 nominations were received with the GCN being given the Runner-Up award in the National Services & Utilities Sector (see press release on http://www.chemsoc.org/gcn for further details).

Commenting on the award GCN Manager, Mike Lancaster said that "it was particularly pleasing to get this award since it comes from outside the scientific community and recognises that chemistry and related engineering disciplines can be carried out in an environmentally benign way. This award has provided an ideal opportunity to get our message across to the general public and will significantly raise the awareness of what we are trying to achieve. I would like to thank all the members who have actively supported us, without your help and commitment we would not have been able to complete many of the programmes which made this award possible." If any one would like further information on the Green Organisation, get copies of all this years winning entries or get information on next years awards please contact Roger Woollens on Tel/Fax 01604 810507.

Hancock Award

A University of Oregon (UO) doctoral student is the recipient of this year’s Kenneth G. Hancock Memorial Student Award in Green Chemistry. Scott Reed, a fifth-year doctoral student in chemistry, won the award for his role in developing the world’s first organic green chemistry instructional laboratory for undergraduates at the UO. Offered by the American Chemical Society to just one student per year, the award carries tremendous prestige for those working in the growing area of green chemistry—in part, because it will be presented in conjunction with the Presidential Green Chemistry Award in Washington D.C. this month.

Reed said winning the Hancock Award added legitimacy to the project. "They (the committee) appreciate that one of the best ways to make a conceptual change in chemistry is to change the way we educate people," he said.

While green chemistry principles are occasionally taught in organic chemistry classrooms, green chemistry experiments did not make it into instructional laboratories until the UO’s pilot green chemistry lab in 1998—a lab which Reed and other graduate students helped design.

Reed got interested in the project after his advisor began researching green chemistry as a way to reduce reliance on the limited lab safety equipment necessary to protect students from the toxic chemicals used in traditional organic lab. Reed’s advisor, Professor Jim Hutchison, solicited the help of fellow professor Ken Doxsee to help design the curriculum.

Interested in environmental chemistry since he was an undergraduate at Bard College, the project immediately appealed to Reed. His role was to research and modify experiments to work within the space and time restrictions of an instructional lab setting. A very big challenge, as it turned out. "For every lab we changed, there was a lot of effort involved," said Reed.

Though green experiments existed in the literature, none of them was tailored to the time restrictions of a student lab. The challenge, said Reed, was to find experiments that would teach the same skills and techniques as a traditional lab, but use more benign chemicals to illustrate those concepts. "The first and foremost thing we did in the course was teach chemistry," he said.

While it is unusual for graduate students to be involved in curriculum-development, Reed applied for and was awarded a special fellowship through the Department of Education, which provided him funding to focus on designing new experiments. Although work on his doctoral project had to be put on the back burner, Reed says the experience was worth the extra effort and will forever influence the way he looks at chemistry.

“Anyone who’s doing chemistry is pulling chemicals off the shelf and anyone can use the concepts of green chemistry in deciding what they pull off the shelf,” he says. “Some day, green chemistry will just be the way chemistry is done.”

One of Reed’s more note-worthy accomplishments is the adaptation of an experiment to synthesize adipic acid, a chemical used to make nylon. Typically, nitric acid is used as the oxidant. An unfortunate byproduct is nitrous oxide, a chemical that contributes to ozone depletion. The green version substitutes a low concentration of hydrogen peroxide as an alternative to the nitric acid, making the experiment much less hazardous. Reed modified and optimized the experiment for the teaching laboratory. The experiment has been accepted by the *Journal of Chemical Education* for publication this year. Reed believes graduate students are an untapped resource when it comes to merging research and curriculum for undergraduates. "I think graduate students are often the most closely connected to current research methods…It's an active part of your day-to-day work. You're always in the lab" he said.

Queens Awards

ICI subsidiary, Crossfield, has won one of the 2000 Queens Awards for Environmental Achievement. The award is for development of the Macrosorb System for treating waste water from textile processing operations. The system removes colour and sufficiently cleans up the water for it to be recycled back to the dye house.

Forum for Environmental and Sustainable Development Awards

The Forum for Environmental and Sustainable Development Awards has been set up to meet the need for a comprehensive database of environmental awards and a consensus on standards and credibility. The Forum is to be run by the Royal Society of Arts, Commerce and Manufacture (RSA) and the UK Government Department of Environment, Transport and the Regions (DETR). The Forum "aims to encourage all means of using well defined and effectively managed awards, and associated publicity, to further the adoption of sustainable development throughout all aspects of the economy and society." In more detail its aims are:

- to draw up a database of relevant award schemes and to assist in making the information available
- to encourage the development of award schemes so as to encourage best practice
- to stimulate discussion about the purposes and criteria for such awards
- to provide an opportunity for the evolution of award schemes
- to see if more publicity, interest and funding can be raised to promote these awards
- to assist in the use of these awards to promote environmental and sustainable development objectives
- to consider action to encourage more entrants for such awards
- to assist the Government in putting its policy objectives as an input to the development of the awards and to help extol the virtues of winners to a wider public
- to consider how awards won by UK entrants can be used to advance UK interests overseas

Over 150 award schemes have already registered with the forum. Relevant schemes can be registered on http://www.sage-rsa.org.uk/project.html

New acylation catalysis chemistry wins award

The Specialised Organic Chemicals Sector Association (SOCSA) in the UK has awarded its 2000 Innovation award to a team of chemists and chemical engineers at Imperial College, London, for their research on the use of fluorous biphase catalysis for Friedel–Crafts acylation reactions. The collaborative research had itself been "catalysed" by the Institute of Applied Catalysis (iAc) (*Chemical Industries Association Press Release*, July 2000).

New business environment award

The 2000 Business in the Community Awards for Excellence include for the first time and Environmental category. The shortlisted entries were from the 3M company, B&Q and Ford. The winner B&Q was commended in many areas including waste management and recycling and is based on its efforts to determine the environmental impact of its products and to develop policies to address them which started in 1990. The winner was announced by HRH the Prince of Wales at the annual Awards for Excellence ceremony in July. The new category is in recognition of the fact that the climate of opinion is moving more in favour of companies which measure and report their impact on the environment-many do this because they now recognise the benefits. All finalists for the Business in the Community Awards for Excellence are showcased on http://www.business-impact.org (*Business in the Community News Release*, June–July 2000)

Polymers from renewable resources

DuPont's bio-based materials business and Tate & Lyle Citric Acid (a subsidiary of the UK company Tate & Lyle PLC) are to jointly develop and manufacture advanced polymers from renewable resources. The new green chemistry process converts carbohydrates into 1,3-propanediol and a commercial scale plant is planned for 2003. The diol can then be reacted with terephthalic acid to make polytrimethylene terephthalate (PPT) which has applications as textiles, upholstery fabrics and resins. PPT is marketed by DuPont under the tradename Sorona whereas rivals Shell call their version of the condensation polymer CORTERRA. PPT is believed to combine the best properties of PET and nylon but has not been commercialised on a large scale as the monomer diol has been regarded as a high price speciality chemical. Both DuPont and Shell have diol manufacturing processes based on petrochemicals but DuPont and Tate & Lyle hope that their renewables-based process will be cheaper. It seems likely that there will be a contest between a green chemistry approach and one based on more conventional chemistry (*The Alchemist*, April 2000)

Greenpeace helps the development of sustainable technologies

Greenpeace is to set up an innovations unit to search for environmental solutions and innovations to assist in the development of sustainable technologies. This follows the organisation's success in working with the organisers of the Sydney Olympics devising environmental guidelines. The sponsors of the Games were challenged to meet the green standards they agreed. Greenpeace was particularly impressed by their success in persuading Coca-Cola to replace ozone-depleting and global-warming refrigerants with Greenfreeze technology.

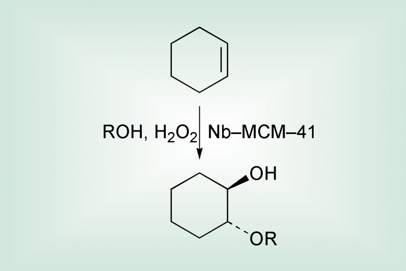
This was developed by Greenpeace and is based on hydrocarbon gases such as propane rather than the HCFCs and HFCs designed to replace CFCs. Greenpeace may do more work on Greenfreeze technology and also expect to work on desalination, sustainable transport systems and renewable energies (*BBC News*, August 10, 2000)

Perspectives

Duncan Macquarrie and Paul Dyson of the University of York, UK, review the latest research in green chemistry

Cyclohexyl glycol ethers

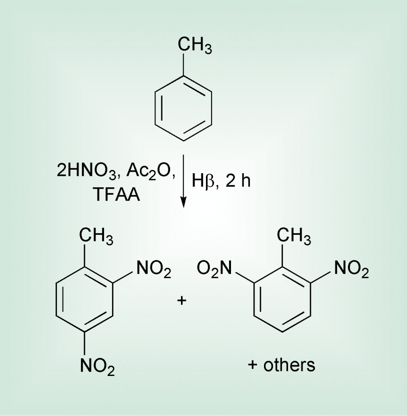
A novel route to cyclohexyl glycol ethers has been discovered by Jishuan Suo and co-workers at the Chinese Academy of Sciences in Lanzhou (*New J. Chem*, 2000, **24,** 569). They prepared novel mesoporous niobium-containing MCM silicas with high structural order, and investigated their catalytic properties. They found that these materials were capable of the conversion, in one step, of cyclohexene, an alcohol, and hydrogen peroxide into an alkoxyalcohol. Thus methoxy- and ethoxycyclohexanols could be prepared with selectivities >90% under mild conditions.



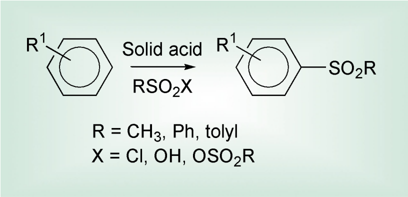
Friedel–Crafts reactions

The Friedel–Crafts reaction remains one of the most useful and versatile methods for the elaboration of aromatic substrates. However, it is also one of the most problematic systems environmentally, with great efforts being expended in the search for replacements for traditional catalyst systems, typically aluminium chloride. Two groups of researchers have recently published progress in this general area of chemistry:

The group led by Keith Smith in Swansea has published details of a novel nitration system, capable of nitrating cleanly strongly deactivated substrates such as nitrobenzene under very mild conditions (*J. Chem. Soc., Perkin Trans. 1*, 2000, 2753) Such processes are traditionally carried out using very powerful and wasteful systems such as nitric acid/oleum mixtures. The new system developed by the Swansea group involves the combination of trifluoroacetic anhydride and nitric acid (an already known, if rarely utilised system) with a zeolite (H-beta). The role of the zeolite appears to be predominantly to control the selectivity of the reaction, rather than acting as a catalyst in its own right. Using this combination of reagents, toluene could be directly di-nitrated in excellent 2,4-selectivity. The 2,4-product is used in a range of applications, and is a precursor to polyurethane monomers. Nitrobenzene, benzonitrile and other deactivated aromatics were also nitrated smoothly.

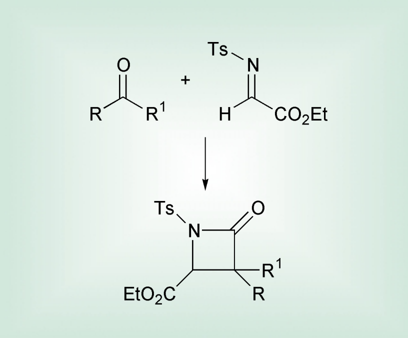


Zeolites and modified clays have also been reported as being excellent catalysts for the sulfonylation of aromatics, leading to sulfones. Researchers in Hyderabad led by Boyapati Choudary have developed a new sulfonylation method based on these materials (*J. Chem. Soc., Perkin Trans. 1*, 2000, 2689). Sulfonic anhydrides were found to be suitable sulfonylation agents, allowing for the reuse of the leaving group via dehydration. However, the use of sulfonyl chlorides led to the highest selectivities in the reactions of toluene (para) and naphthalene (beta)—up to 99%, curiously, in contrast to the work of Smith, the nature of the catalyst did not appear to have any influence on these systems.



Chiral β-lactams

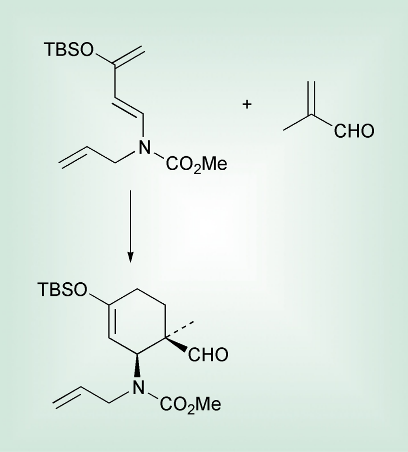
The synthesis of β-lactams is of great importance in pharmaceutical chemistry, with many applicational areas relying on a supply of chiral β-lactams. Despite this, there is a lack of a suitable catalytic process for their formation, the majority of routes relying on the use of chiral auxiliaries. Thomas Lectka and colleagues form the Johns Hopkins University in Baltimore have now published details of such a catalytic route (*J. Am. Chem. Soc.*, 2000, **122**, 7831). Their method involves the coupling of a ketene with a non-nucleophilic imine. They showed that such a process required the use of an amine as a nucleophilic catalyst, and then extended this to involve chiral quinine-based amines in an enantioselective variant of the process.



Good yields, excellent ee (>95%) and high diastereoselectivities (99/1) are obtained using 10 mol% of catalyst.

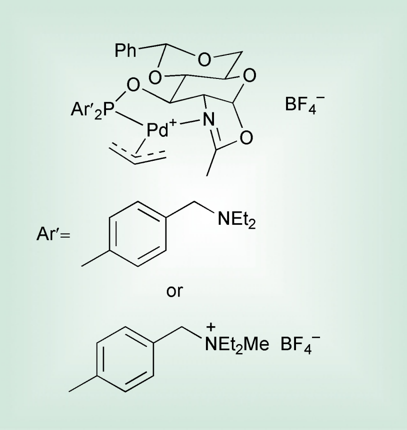
Diels–Alder reactions

The Diels–Alder reaction is another cyclisation reaction of great importance in synthetic chemistry and, being an addition process, has the potential for being very clean. Viresh Rawal and co-workers at the University of Chicago have published an enantioselective version of this reaction using chiral Lewis acids (*J. Am. Chem. Soc*., 2000, **122,** 7843). They have utilised such reactions in the synthesis of natural products, and this communication details their work on an enantioselective route to a key intermediate. They have used a Cr(III) salen complex, derived from 1,2-diaminocyclohexane as chiral unit, and applied this to the synthesis of the amino-aldehyde shown. In a relatively slow reaction (several hours to days were required) good enantioselectivities were obtained (77–93%) and high yields were obtained. Given that the catalyst is relatively flat, the degree of enantioselection obtained was impressive.



Biphasic systems

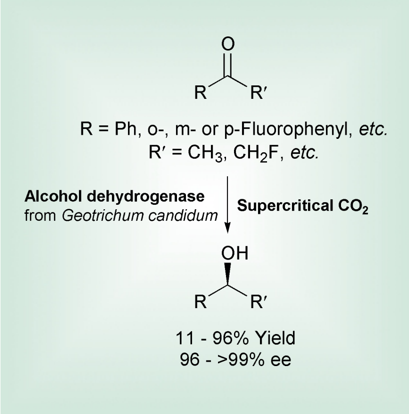
The design of catalysts and catalyst ligands with a view not only to excellent activity and selectivity, but also to their solubility and recoverability in biphasic systems is becoming more important. A clever example of such a designer ligand has been published by Ohe, Uemura and co-workers in Kyoto. (*J. Org. Chem.*, 2000, **65**, 5197) Their ligand, based on natural glucosamine, is a bidentate P,N ligand, suitable for the co-ordination of Pd. The catalyst is water soluble, and can be used in aqueous systems, thanks to the quaternisation (or protonation) of a remote amine group. Good yields and enantioselectivities were obtained in the aqueous allylic nucleophilic substitution reaction, and catalyst recovery and reuse were demonstrated. Similar reactions can be carried out in organic solvents, and the catalyst then extracted into water by protonation of the remote amine group, followed by neutralisation to give the organic soluble catalyst back.



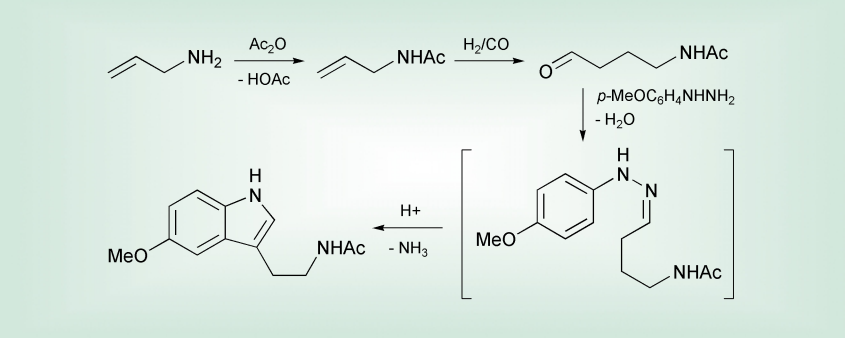
Roger Sheldon and his co-workers at Delft University have published a very concise and efficient synthesis of melatonin (*Chem. Commun.*, 2000, 1363) (scheme below). They used an aqueous-organic biphasic system to carry out the hydroformylation of allylacetamide. They found that the hydroformylation worked very well with a water-soluble Rh-phosphine, but the product aldehyde had a great affinity for water, making separation difficult. The researchers solved this problem by using a conventional, hydrophobic, Rh complex in toluene, and extracting the product into the second (aqueous) phase. The aqueous phase could be used directly in the final step of the synthesis without isolation or contamination from Rh.

Supercritical fluids

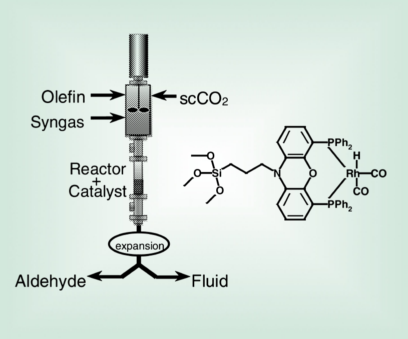
The advent of supercritical fluids (SCFs) as novel reaction media has provided many opportunities for clean chemical synthesis, and the range of methods which function well in SCFs is steadily increasing (*Green Chem*., 2000, **2,** 127, 161 and *Green Chem*., 1999, **1,** 65). The use of enzymes in SCFs has also been demonstrated, particularly hydrolases. A paper from Tomoko Matsuda and his group at Ryukoku University in Shiga (*Chem. Commun*., 2000, 1367) describes the extension of this concept to alcohol dehydrogenase enzymes. They used cells from Geotrichium candidum to reduce a series of ketones to the corresponding alcohols in high efficiency and with excellent ee (96–99%). The use of supercritical carbon dioxide as reaction medium is claimed to be better than water, due to the difficult separations encountered using this class of enzymes in aqueous systems.



The combination of heterogeneous catalysis in a supercritical fluid continuous flow reactor has been elegantly demonstrated by the group led by Martyn Poliakoff at Nottingham

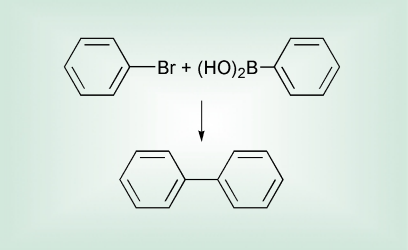


University (*Chem. Commun.*, 2000, 1497). They used a silica-supported diphosphine-Rh complex to carry out the hydroformylation of oct-1-ene with a high degree of selectivity. Linear to branched ratios for the aldehydes produced were around 40:1 at reasonable levels of conversion. Recycling of the octene appears to be easily achievable, as it is easily recoverable by controlled depressurisation after reaction. Catalyst lifetime was good, consistently giving rates around half that of the homogeneous equivalent over many hours.



Suzuki cross-coupling

The Suzuki cross-coupling reaction between arylhalides and arylboronic acids is widely used in organic synthesis. Tom Welton and his team at Imperial College, London, have been investigating the ambient temperature ionic liquid 1-butyl-3-methylimidizolium tetrafluoroborate as a medium for conducting the Suzuki reaction using $Pd(PPh_3)_4$ as the catalyst (*Chem. Commun.*, 2000, 1249). They have compared the catalytic activity in the original solvent system employed, *viz.* toluene-water-ethanol, with the ionic liquid and found dramatic enhancements. For example, an increase in yield from 88% in 6 hours to 93% in 10 minutes is achieved for the coupling of bromobenzene and phenylboronic acid. Furthermore, the process works with a reduced catalyst concentration and there does not seem to be any appreciable decrease in activity with repeated use. The salt by-products generated in the reaction can be extracted into water before reuse of the ionic liquid-$Pd(PPh_3)_4$ medium.



In the same issue of *Chemical Communications* (2000, 1237), David Haddleton and his group at Warwick use a related ionic liquid for copper(I) mediated radical polymerisation of methyl methacrylate.

FOCUS ON.....green chemistry at the University of Strathclyde

In visiting various chemistry and chemical engineering departments throughout the UK for this "Focus On" series it has become increasingly evident that there is a lot more green chemistry research going on than most people realise. Nowhere is this more true than in the Department of Pure & Applied Chemistry at the University of Strathclyde in Glasgow, UK, indeed the whole journal would be needed to do full justice to the large amount of work going on in this under-recognised centre of green chemistry excellence.

Polymer-supported reagents & catalysts

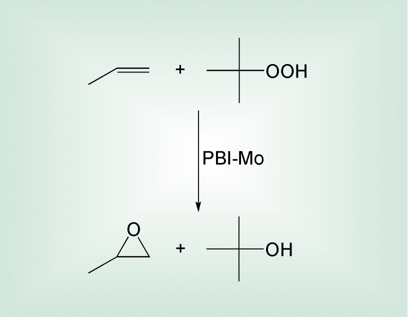
The history of the Department's involvement with clean technology goes back to the seventies with the pioneering work of David Sherrington, Professor of Polymer Chemistry, well before the term 'green chemistry' came into use. One of Sherrington's main interests is in the use of polymers to support catalysts and reagents. The potential environmental benefits of supported catalysts and reagents have now become widely recognised and include:-

- more efficient separation and purification of products
- ease of recyclability and reduced waste compared to homogeneous systems
- possible rendering of noxious species innocuous

Although interest in polymer supports has grow significantly in recent years they are still less widely studied than traditional inorganic supports. Sherrington readily acknowledges the advantages and dis-advantages of both, but has been inspired by the potential polymers offer for tailoring the support structure to specific reaction types, *e.g.* asymmetric synthesis.

Alkene epoxidation is an area of current interest to Sherrington. With the exception of ethylene oxide, the greenest route to epoxides—direct oxidation of the alkene with oxygen in the presence of a catalyst—has not been possible, largely due to substituted alkenes being more reactive towards allylic oxidation. The answer to many epoxidation problems has been to use *tert*-butyl hydroperoxide or hydrogen peroxide with a homogeneous metal catalyst such as those based on Mo(VI) and Ti(IV). Sherrington's group have been studying the immobilisation of such metals on polybenzimidazole (PBI), a thermal and oxidatively stable polymer to which metals can be readily attached via treatment with their acetylacetonate (acac) complexes. Using propene as substrate, *tert*-butyl hydroperoxide as oxidant and PBI-Mo as catalyst virtually quantitative yields of propylene oxide have been achieved with no detectable leaching of metal and excellent catalyst recyclability.

In an extension to this work, using cyclohexene as substrate, the highly complex nature of the underlying chemistry has been demonstrated. By varying the catalyst (*e.g.* PBI–Cu, PBI–Ti, PBI–Fe) and reaction conditions, different ratios of alcohol, ketone and epoxide could be obtained. More interesting however is the fact that less than stoichiometric amounts of peroxide are required when the reaction is carried



out in air, since oxygen is also being involved in the reaction.

For the speciality chemicals and pharmaceuticals industry enantioselective epoxidation is an important reaction, both to control costs and to minimise waste. Chiral catalysts such as Jacobsen's chiral Mn^{III}(salen) complex have played an important role in enabling such reactions to be carried out; however further green and cost benefits could be achieved if such catalysts could be heterogenised. In an elegant piece of work Sherrington has immobilised the catalyst on styrene- and methacrylate-based polymers and managed to achieve almost the same enatiomeric excess as obtained with the homogeneous systems.

Sherrington's hope, one day, is to see a large bulk chemical process 'greened' by use of a polymer-supported catalyst or reagent and he is actively involved with a number of large companies such as BP Amoco in trying to achieve this goal. One of the main obstacles is the current cost of the base polymer resins. He believes that initial applications will be in the higher added value end of the market which will pave the way for larger volume resin production, so reducing costs.

Alternative reagents

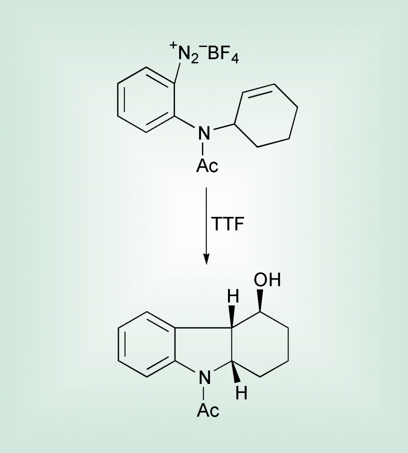
Although tin is a fairly environmentally friendly metal and is finding increasing use as a replacement for lead, the story is very different for organotin compounds. Many organotin compounds are highly toxic and have been banned in applications such as antifouling paints for boats. Tributyltin hydride has long been used as a versatile radical generating reagent but its toxicity, coupled with the difficulty of removing tin residues from the product, has prevented widespread industrial use, particularly in the synthesis of medicines. John Murphy, Merck-Pauson Professor is at the forefront of research into finding environmentally friendly alternative ways of forming carbon-carbon bonds using radical chemistry.

Over recent years Murphy's group have been studying two main types of radical reactions, those that lead to reductive termination—as obtained with Bu_3SnH, and those that give functionalised products (oxidative termination). The latter reactions have been given the elegant title of "Radical-Polar Crossover Reactions" so-called because the mechanism involves not only radical generation and subsequent reactions but a final non-radical polar step.

The reaction centres around the use of an easily oxidised sulfide which transfers an electron to an electrophile (typically arenediazonium salts have been used). Tetrathiafulvalene (TTF) was the chosen sulfide due to its ease of oxidation and commercial availability. After demonstrating the success of the approach on model systems the real test was to demonstrate the viability in synthesis of complex molecules. The naturally occurring alkaloid aspidospermidine was the target molecule of choice with the crucial radical step being the ring forming reaction shown below. The results were good, the required product being obtained as a single stereoisomer in 65% yield.

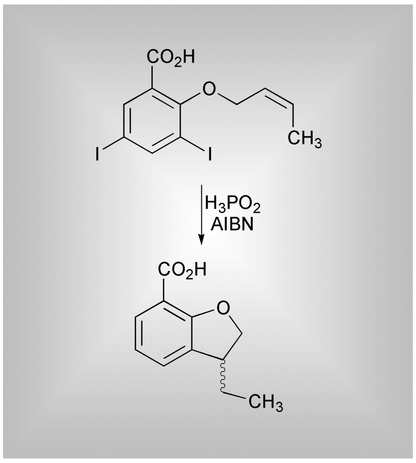
The group have subsequently demonstrated the widespread usefulness in even more complex systems and have 'greened' the reaction further by improving the ease of recovery of the sulfide by supporting TTF on polymer or making water-soluble analogues.

The reductive termination route involves use of phosphorous centred radicals as derived from hypophosphorous acid or its *N*-ethylpiperidine salt. Although these reagents had been used by Barton and others for defunctionalisation of halides they had not been used in carbon–carbon bond forming reactions, possibly due to the perceived reactivity of the phosphorus radical. Working with Merck, Murphy's group demonstrated the potential usefulness and versatility of this reaction in both aqueous and organic media, using, for example, alkyl bromide or aryl iodide substrates. A typical transformation which proceeds in well over 70% yield is shown opposite.



A patent has been applied for covering this work and, for Stephen Graham the Merck CASE student who started it all, there has been the added bonus of receiving a number of prizes from organisations such as Pfizer, RSC and SCI.

John Murphy's group at the University of Strathclyde.



Much of the early work in this area was sponsored by EPSRC under the Clean Technology programme. Murphy believes that periodic programmes such as this are very important in providing an impetus to move into new fields and are especially important in areas such as clean technology which have such potential wide-spread benefits.

The Green Light

Other than the EPSRC programme mentioned above the other main initiative in the area has been the establishment of EPSRC-RAEng (Royal Academy of Engineering) Clean Technology Fellowships. The basic concept was to release a leading academic from teaching duties for a period of 3 years to enable them to concentrate on research and promotion. Dr. Ian Dunkin was one of the first recipients of such a fellowship which he got to promote the wider use of photochemistry in industry, particularly for chemicals manufacturing. Under this remit Dunkin has, amongst other things, been identifying current industrial processes where photochemistry could offer a cleaner alternative as well as developing novel photochemical reactors to overcome common disadvantages of photochemical processes such as fouling. The potential advantages of the photochemical approach to clean technology are many and include:

- reactions are activated by light, minimising reagent usage.
- activation energy is targeted at the specific molecule, potentially saving energy overall.
- selectivities are different to thermal reactions, and in favourable cases this can be exploited to give fewer by-products and higher yields.

One of the main things to come out of Dunkin's fellowship is a collaborative project with the speciality chemical company A H Marks. Much of this work is commercially sensitive but in broad terms the work is aimed at improving the selectivity and reducing by-products formed during the chlorination of propanoic acid using photochemical technology.

One of Dunkin's firm beliefs is that there is much to be gained by working in multi-disciplinary teams, especially those involving a combination of chemists and chemical engineers. It is no surprise therefore that he is involved in several collaborative projects with chemical engineers at Strathclyde and elsewhere. These projects include development of novel photochemical reactors which prevent fouling on the surface of the light source and the production of high efficiency gas separation membranes.

This latter project is being carried out in conjunction with Air Products Inc. and revolves around improving the gas separation selectivity (*e.g.* N_2 /O_2) above the intrinsic value of the amorphous polymer by tailoring the molecular orientation during the spinning and extrusion process. Dunkin's role in the group is in characterising the membranes using polarised Raman spectroscopy which leads to a greater understanding of how fabrication alters molecular structure. A range of polymers including polysulfones, polycarbonates and polyimides have been successfully studied. The green advantages of this work lie mainly in the reduced energy use compared to cryogenic separation processes.

Dr Charles Gordon is also an indirect beneficiary of the EPSRC–RAEng Clean Technology Fellowship, in so much as he moved to Strathclyde to take over Ian Dunkin's teaching duties, more recently he has been awarded a Royal Society of Edinburgh / BP Research fellowship to study photochemistry in ionic liquids. Coming from Ken Seddon's group at Queen's University Belfast, Gordon is starting to carve out his own niche area in ionic liquids research. The potential environmental benefits of ionic liquids centre around their very low vapour pressure and need no introduction to readers of *Green Chemistry*.

Photochemical reactions in purely ionic media have been little studied and the hope is that the environmental benefits of photochemistry and ionic liquids can be compounded. Furthermore, such investigations are often solvent-sensitive, and may therefore be used to provide information about the nature of ionic liquids as reaction solvents. Systems which Gordon is currently studying include:

- the influence of different ionic liquids on a range of solvatochromatic dyes.
- electron transfer between photoexcited $[Ru(bpy)_3]^{2+}$ and methylviolgen dication.
- triplet energy transfer between photoexcited benzophenone and naphthalene.
- the behaviour of photo- and thermochromic spiropyrans in ionic liquids.

The results gained are already providing useful information about how the behaviour of ionic liquids may be related to that of more conventional organic solvents.

Also using light to produce a cleaner environment is Professor Andrew Mills whose interest lies in semiconductor photocatalysis, in particular its use to destroy organic pollutants in air and water—photomineralization. The basic principle of photomineralization is that when light of a wavelength greater than the bandgap[1] energy is shone onto a semiconductor such as titanium dioxide, in the presence of oxygen, sufficient energy is formed to generate reactive radicals such as hydroxyl and peroxy-radicals which completely oxidise organic substrates to carbon dioxide and water. Any hetero-atoms present in the organic substrate are converted to the corresponding mineral acid.

$$\text{Organic pollutant} + O_2 \rightarrow CO_2 + H_2O + \text{mineral acids}$$

The technology is developing at a rapid pace with commercial systems now being developed in Japan and elsewhere using sunlight and low cost sources of UVa to provide clean water and reduce air pollution. One spin-off from the work is the window or light diffuser that needs much less frequent cleaning. A very thin surface layer of TiO_2 would prevent contamination by grease and oil droplets by breaking them down to CO_2 and H_2O. For this approach to be viable very thin layers of TiO_2 are required such that the transparency properties of the glass are not adversely altered. Mills, in

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[1] E_{bg}—the difference in energy between the highest occupied band and the lowest unoccupied band, *cf.* HOMO and LUMO at the molecular level.

conjunction with Professor Michael Hitchman is looking at chemical vapour deposition techniques to provide such coatings. In addition, the Strathclyde group are working with industry at improving the efficiency by reducing the bandgap energy such that light in the visible region of the spectrum can be used to drive the process. Semiconductor morphology and the presence of metals such as Cr and Pt can all play a part it improving the overall efficiency. Interestingly, work carried out by this group has established that semiconductor photocatalysis can be used for carrying out cold destruction of explosives such as TNT and chemical weapons such as Sarin!

Biotransformations

Biotransformations - using enzymes to carry out chemical reactions - are a frequently quoted class of green reactions offering benefits such as improved selectivity, reduced use of reagents and organic solvent-free processes. On the other hand many such reactions are slow, only take place in dilute solutions and produce large waste streams. Professor Peter Halling has a keen interest in the application of biological catalysts and focuses on solving general fundamental problems applicable to a wide range of processes. Halling is another keen advocate of the importance of the multi-disciplinary approach to problem solving and works closely with colleagues from the Process Engineering and Bioscience & Biotechnology departments as well as with several international collaborators.

Much of Halling's recent work centres on improving reaction and reactor efficiency by, for example, working in solvent free conditions or by improving enzyme activity. Freeze-dried enzyme powders are often used because of their ease of preparation. These materials however usually exhibit low activity. The alternative cross-linked enzyme crystals are more active but very expensive. The Strathclyde group have recently disclosed a simple procedure for producing enzymes of high activity based on immobilisation on silica gel followed by dehydration by repeated washing with propanol. By using such a technique the activity of the transesterification enzyme substilisin Carlsberg was increased 1000 times compared to the freeze-dried powder. In many ways esterification reactions are ideally suited to biocatalysis but they need to be carried out in largely anhydrous conditions and water produced during the process must be removed to drive the equilibrium forward. Halling has been working with engineering colleagues to find efficient ways or removing this water and has found that a controlled leak of air into an evacuated reaction is an economical way of achieving this goal.

Other means of improving the efficiency of enzyme reactions being studied include development of virtual solid phase reactions (*e.g.* for aspartame synthesis) where enzyme activity as well as reactor design are vitally important. Use of supercritical solvents for biocatalysis is also an area of interest to Halling, who is about to start exploratory work in the area with Susana Barreiros at the University of Lisboa.

From the wide range of topics being studied and the number of people involved, Strathclyde can justifiably claim to be a centre of excellence in green chemistry research. On the teaching front the department has adopted the approach of introducing relevant 'green' material where appropriate throughout the undergraduate course. This approach is used to emphasise the fact that green chemistry is not a specific topic to be taught in isolation but is a set of underpinning principles.

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Green Industrial Application of Ionic Liquids–a NATO Advanced Research Workshop, Crete, Greece (12–16 April 2000)

Professor Robin D. Rogers of the Center for Green Manufacturing at The University of Alabama, USA, reports on a recent workshop

In the first international meeting dedicated to the study and application of ionic liquids (IL) as solvents, 41 scientists and engineers from academia, industry, and government research laboratories met in Heraklion on the island of Crete to discuss the current and future status of the application of ionic liquids to new green industrial technologies. They were joined by 6 industry observers and 4 student/staff helpers. The full program, scientific abstract, attendee list, and group picture can be accessed via the website created for this ARW at http://bama.ua.edu/~rdrogers/NATO.

The workshop began with a plenary lecture on green chemistry by Professor John Warner (University of Massachusetts-Boston) followed by three-and-a-half days of intensive lectures and discussion on the current status of ionic liquid research and application. Topics covered included industrial needs in green chemistry, current industrial applications of ionic liquids, separations, electrochemistry, novel chemistries in ionic liquids, green catalysis, and the status of East–West collaborations.

The last day-and-a-half were devoted to roundtable discussions meant to distill the workshop's content into major recommendations of the ionic liquid research community. The three roundtables included:

- outlining industrial priorities, needs, and challenges in green chemistry
- drafting ionic liquids research priorities to meet the green needs of the chemical industry
- developing protocols to enhance East–West collaborations in ionic liquids research.

Roundtable 1, Outlining Industrial Needs and Challenges in Green Chemistry

This roundtable was facilitated by Leo Manzer (DuPont), John Warner (University Massachusetts-Boston), and Chris Adams (The Institute of Applied Catalysis). This roundtable discussed industrial needs and challenges in general without superimposing a discussion of ionic liquids. Industry representatives were present from a wide range of industry including bulk chemicals, fine chemicals (pharmaceutical, agriculture, and specialty), and petrochemicals. Additional consideration was given to energy (battery, solar, fuel cell, and nuclear) applications, remediation, and education. Many of the outcomes (below) were similar to those developed in other exercises of this type within the United States, for example the Department of Energy, Office of Industrial Technologies Industries of the Future Program (http://www.oit.doe.gov/industries.shtml), specifically, Vision 2020 and the U.S. chemical industry (http://www.doe.oit.gov/chemicals/), and in the United Kingdom, for example, Fore*sight* (http://www.foresight.gov.uk); but differences arose from the perspectives of the participants.

Major industrial challenges for sustainability to come out of Roundtable 1 included:

- reducing water use
- increased energy efficiency
- reducing reliance on fossil fuel feedstocks, increased use of renewables
- a change in basic economics to include sustainability as a major criterion

Industrial representatives provided several major current challenges or 'Holy Grails' that need to be solved whether with the use of IL or some yet to be developed technology. These included drastic improvement in such reactions as:

- NO_x compounds to nitrogen and oxygen (or the inverse)
- benzene to phenols
- direct amination to aniline
- cheap feedstock utilization (*e.g.*, butadiene directly to desired products)
- improved C1 chemistry for CH_4 or CO_2 feedstocks
- enabling technologies for lignin or sugar utilization as general feedstocks.

Separations were also highlighted as an enabling technology. New separations that enable currently difficult or impossible separations efficiently or can be used to easily separate unused feedstocks from valuable/non-valuable byproducts would have a tremendous impact on sustainable development. One pot (multi-step) syntheses and separation and the elimination of toxic chemicals in processing or products were also cited as important needs.

Roundtable 1 identified several potential opportunities for major impact in sustainable industry. These included methods for major improvements in:

- alkaline activation
- selective oxidation and reductions (including asymmetric synthesis)
- reducing the number of synthetic steps
- improved atom economy
- electrocatalysis
- new enzymatic pathways
- new biocatalysts
- nontoxic batteries
- efficient fuel cell technologies
- the development of personal electricity systems.

It was also pointed out, however, that industrial R&D needs may differ substantially from the R&D conducted in many academic laboratories. In industry there is a need for speed, and better information is needed for faster decision making. In this regard, enabling technologies include:

- data for complete modeling
- Safety/Health/Environment (SHE) data
- complete information on biodegradation and the fate or transport of new solvents in the environment.

The discussion also included ways that industry and the academic R&D culture could work more closely together in the development of new environmentally-benign technologies. There is currently a perceived shift in industry away from R&D and an increase in the reliance on universities for long-term (and often short-term) R&D. Strategic partnerships can enable step change functions in the development of new technologies, but the applied/fundamental research balance must be maintained at the university level. A danger in the creation of partnerships is the protection of all data and information. Unless this is readily available to the R&D community, further developments will be hampered.

Finally Roundtable 1 tackled the implications of education and communication on the development of sustainable industrial technologies. The chemical industry of the 21st century needs technical personnel trained for today's environment (team oriented, problem solving, thinking "green"). Public information and misinformation offer conflicting views of the chemical industry. Much that is perceived to be bad about the industry may not currently be true. The public must be educated about the benefits of chemistry and science/engineering literacy must be a high priority in education.

Roundtable 1 then set the tone for Roundtable 2 which highlighted where ionic liquids might make an impact in reaching these goals. Chris Adams pointed out that new processes must meet the needs of the present without compromising the ability of future generations to meet their needs. Sustainability has to be economic, social, and political. New *processes* should be developed, not just new chemistry; networks of researchers should be developed; information should be structured for maximum use; and people must be the agents of change. David Moody (Avecia) suggested that the potential benefits of IL are as an enabling technology, allowing process intensification and reduced environmental impact. He suggested that to realize the benefits of IL, a research agenda must be developed whose product would be a small family of the 5–10 'best' IL. From this group of IL, efficient syntheses must be developed; good product isolation must be possible; and recycle of solvents is critical.

Roundtable 2, Drafting Ionic Liquid Research Priorities

This roundtable was facilitated by Ken Seddon (Queen's University Belfast), David Moody (Avecia), and Robin Rogers (The University of Alabama). Initially the group reviewed the outcomes of Roundtable 1 and the perceived major challenges (Holy Grails) of sustainable development. While no one suggested IL are ready to completely solve all these challenges, participants pointed out where IL could contribute to almost all of these areas. An example was given of current high temperature molten salt conversion of benzene to phenol and the use of IL in the fractionation of biomass. New separations techniques appear to be a particular fruitful area of potential application of IL.

The group next tried to develop properties for an 'ideal' IL including low cost, water stability (as well as stable to solvents, products, *etc.*), of low toxicity and environmental impact, non-corrosive, and recyclable. Industry representatives suggested a viscosity of less than 100 centipoise and thermal stability to 800 °C (although a lower limit of ~200 °C would be fine for general use) as additional ideal requirements. It was suggested that these ideal characteristics are not unique to IL, but apply to other new materials/solvents as well. Perhaps the biggest outcome of this discussion, however, was that to encourage applications of IL in industrial processes, this ‘ideal’ IL should be free of intellectual property constraints!

Discussion next turned to criteria needed to assess IL. Toxicity, bioaccumulation data, (safety/health/ environment impacts) and cost/benefit, economic, and life-cycle analyses were perceived as high priorities. Physical and thermodynamic properties and constants, transport properties, miscibilities, and purity assessment were highlighted as immediate needs.

Several challenges to the IL field were discussed. Regulatory issues, manufacturing rates/availability, and intellectual property constraints were discussed as current barriers to implementation of IL technologies. There are also real needs for a more fundamental understanding of ionic *vs.* molecular solvents and increased international cooperation and communication of results.

In general it was felt that IL represent a new way of thinking about solvents. The research is intrinsically worth doing for advancing science with the expectation that something useful *may* be derived. The field is experiencing rapid growth and appears to be at a point where scientists/engineers/ business personnel can work together from the beginning in a new (or rediscovered) area, in a new paradigm of green chemistry and sustainable industry.

It was also discussed that new scientific and engineering groups are needed in the field. Organic chemists and chemical engineers were specifically cited as examples, but in general it was noted that many areas of expertise are available and each group should work toward their own area and not try to do everything. Public access of data (*e.g.*, physical properties) and a general collaborative model were suggested as methods needed to encourage both new R&D personnel to enter the field and new industrial interest in IL technologies.

Roundtable 3, Developing Protocols to Enhance East–West Collaborations in Ionic Liquids Research

This roundtable was facilitated by S. Volkov (Ukrainian National Academy of Sciences), S. Boghosian (FORTH/ICE-HT), and J. Kotlán (VÚOS a.s). S. Boghosian began the discussion with a thorough description of the NATO Science Program and the mechanisms for developing collaborative research programs between NATO and NATO-Partner countries. Subsequent discussion brought to light a perceived major barrier in the unequal economic and industrial development between NATO and Partner countries. Implementation of IL technologies in the East will require major technological as well as cost advantages. R&D collaboration between East and West must take into consideration the current research climate in the Partner countries.

Major outcomes of the workshop

These included the following:

- Ionic liquids are intrinsically interesting and worthy of study for advancing science (ionic *vs.* molecular solvents) with the expectation that something useful *may* be derived from their study.
- Combined with green chemistry, a new paradigm in thinking about synthesis in general, ionic liquids provide an opportunity for science/engineering/ business to work together from the beginning of the field's development.
- Readily available, well-characterized ionic liquids, free of intellectual property, are needed to encourage development of applications.
- Toxicity, biodegradation, bio-accumulation, safety, health, and environment (SHE) impact data are needed immediately.
- Ionic liquid research should include cost/benefit, economic, and life-cycle analyses.
- Regulatory road blocks to ionic liquid implementation should be tackled now.
- A public (free), verified, web-based database of physical, thermodynamic, and related data (*i.e.*, not process specific) is needed, and work should start immediately on identifying the best methods to accomplish this.
- There is an urgent need to increase the number, but especially the areas of expertise of ionic liquids researchers. A model of open collaboration needs to be encouraged.
- International collaboration and communication/education regarding the results are needed.
- A brochure should be developed to advance the understanding of ionic liquids and their applications.
- A NATO Advanced Study Institute should be held dedicated to all facets of the study and application of ionic liquids from scientific, engineering, and business perspectives. This meeting should occur no earlier than Spring 2002.

Chlorine: the only green element – towards a wider acceptance of its role in natural cycles

Review

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Approximately 2000 compounds of chlorine, both inorganic and organic, are known to be produced, transformed, transported and degraded in a range of natural geological, chemical or biochemical processes in most of the earth's environmental compartments. Chloroform, chlorophenols, chloroacetic acids and polychlorinated dibenzo-*p*-dioxins and dibenzofurans, long believed only to have arisen from man's activities, have significant natural sources, some of which predate industrialization. The presumption that such materials are solely man-made must now be seen as incorrect. In fact, sufficient is known to suggest that natural cycles involving both organic and inorganic chlorine should be more widely recognised. Their characteristics should be more fully understood so as to put emissions of related synthetic materials and associated control and remediation measures into better context. The role played by organochlorine compounds, synthesised and utilized by a range of aquatic and terrestrial organisms (including humans) and the biosynthetic pathways leading to their formation and transformation are areas of research worthy of further study.

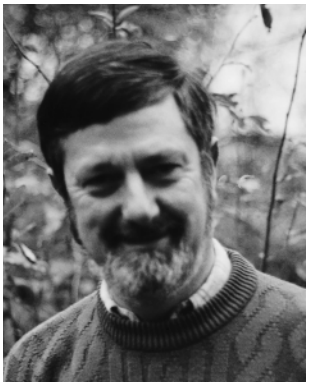
1. Introduction

Most scientists, particularly those who have prepared, handled or simply seen the seventeenth element of the periodic table, will judge the headline title of this review to be a factually correct statement (notwithstanding unsubstantiated claims[1] to the contrary). To others, particularly those who have been concerned with the environmental impact of some persistent, bioaccumulative and toxic compounds containing chlorine, the title may appear flippant, provocative or even heretical. Yet others, aware of my former industrial affiliation, might search for some ulterior motive in the sub-text of my survey. (Indeed, the very language in which environmental issues are presented and debated has itself become a separate topic for academic study.[2])

That all these reactions are possible says much about the public perception of chemicals in general and of those containing chlorine in particular. For example, while water purification and disinfection has been ranked 46th by Life Magazine[3] in its top one hundred advances of the millennium, concerns arising from epidemiological evidence,[4] suggesting a statistically weak association between the consumption of chlorinated drinking water and liver cancer, led the authorities in Peru, presuming a causal link, to stop chlorinating drinking water. The cholera epidemic[5] that ensued killed more than 10 000 people. Fortunately, more rational judgements about the balance of benefits arising from the use of chlorine are beginning to appear.[6–12]

The purpose of this review is to encourage a more informed awareness of the fascinating chemistry and biochemistry of chlorine in the natural world (for a series of short accounts see ref. 13) and, thereby, to correct the erroneous perception that all organochlorine compounds found in the environment are present solely as a result of man's activities. The survey will cover the variety, abundance, sources, and functions of

Neil Winterton joined ICI's Corporate Laboratory in 1973 after 8 years' research in inorganic reaction mechanisms, organometallic and coordination chemistry at University College, London, the University of North Carolina at Chapel Hill and the University of Warwick. He moved to ICI's Mond Division (later ICI Chlorchemicals) in 1977 where he worked on product R&D on a range of halogenated materials, for which he was appointed a Research Associate in 1985. His interests at ICI developed to include C_{60} chemistry, applications of ionic liquids, cleaner technology and the natural chlorine cycle. He was a founding member (subsequently Deputy Chairman) of the Industrial Advisory Board of the Questor Centre, the Queen's University of Belfast (1988–1998), Visiting Industrial Professor at Queen's (1993–1994) and a member (later Chairman) of the Natural Chlorine Cycle Working Group of Euro Chlor (1995–1999). He joined the Leverhulme Centre for Innovative Catalysis in the Department of Chemistry, University of Liverpool, in 1999, to pursue his interests in industrial and catalytic applications of ionic liquids, cleaner technology and high-throughput testing.



Green Context

The area of chlorine and its compounds has become a very contentious issue in the last few years, with conflicting claims and counterclaims. This review represents a thorough and comprehensive study of the subject area from many points of view, and is a carefully thought out and dispassionate piece of work. The article makes clear the issues which must be addressed in evaluating the fate of chlorine and its compounds, by putting all the evidence in context. *DJM*

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chlorine-containing compounds, inorganic and organic, present naturally in the environment now and over geobiological time. To provide a further perspective for the current debate regarding chlorine and chlorinated chemicals the many significant developments in the natural chemistry of this element and its compounds are discussed, including new reports that the element itself has unequivocally been directly detected in the unpolluted marine atmosphere,[14] that organic compounds containing covalently bound chlorine are themselves synthesised in the human body[15] and that the 3000th naturally occurring haloorganic has been described[16] (for it is not possible to give a satisfactory review of the natural chemistry of chlorine without some mention of that of other halogens, particularly bromine and iodine).

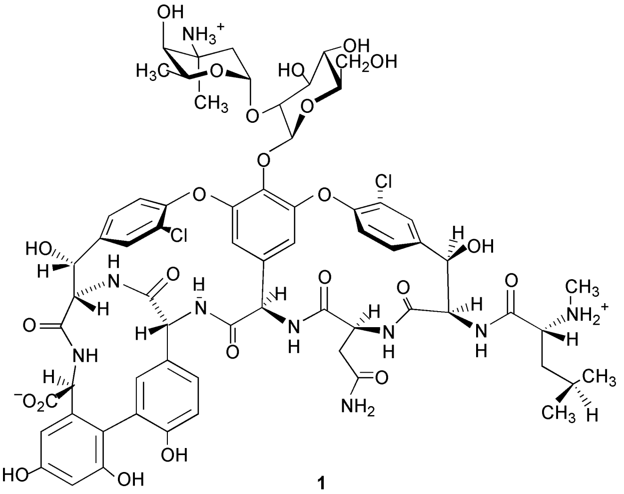
The detection in the environment of certain persistent organochlorine compounds[17–20] and their association with deleterious environmental and toxicological effects[21–23] has led to their control and where necessary their elimination. The conflicting issues associated with the actual or suspected consequences of the presence of these compounds in the environment are exemplified in a series of brief articles[24–28] (though even here the role of naturally produced materials receives no mention). The heightened public concern has coincided with, and may have been responsible for, a shift from the historical perspective of concern largely for man's welfare to one of regard for adverse effects (or possible or potential effects) on all living things, the broad acceptance of which is the legacy of the efforts of the ecological and environmental movements over the last forty or so years.

While the proper regulation of persistent, bioaccumulative and toxic chemicals is necessary and, in the case of organochlorine compounds, is having the desired effect in reducing the measured levels of such compounds in biota[29–32] (and while also accepting the need for further environmental monitoring[33, 34]), the closure of the chlorine industry would not achieve the avowed purpose of its proponents, namely, the elimination of **all** chlorinated organics (nor even all the compounds of concern) from the environment. The latter would also require the elimination of the many life-forms, fish, sponges, algae, phytoplankton and other marine dwellers, insects, worms, freshwater amphibians, flowers and vegetables, fungi and even humans, that produce and emit them naturally.

In addition, opportunities for the beneficial application of organochlorine compounds, such as in the treatment of disease, would be lost. For instance, the use of existing antibiotics, such as vancomycin **1**, and new compounds currently in clinical trials against HIV, 935U83 **2**[35] and Efavirenz **3**[36,37] as well as lead compounds against certain mycobacteria (such as the pathogen responsible for tuberculosis) maracen A **4**[38] and against tumours, (±)-halomon **5**,[39] or the cryptophycins **6**[40] and **7**[41] all of which contain chlorine, would have to cease.

The very detection of a material claimed to be a pollutant in the environment now leads to calls for immediate controls. Bearing in mind the exquisite sensitivity of analytical techniques (for instance, it is now possible[42–44] to estimate one part of polychlorinated dibenzo-*p*-dioxins and furans in 10^{18} (0.001 ppq)) and the likelihood that further reductions in the limits of detection will be achieved, the challenge to government and regulators will be to assess the significance of such scientific evidence, and the weight to be attached to any conclusions derived from it, in the context of risk assessment and management, also bearing in mind the impossibility of eliminating all risk and the misdirected costs of seeking to do so.

It is also now quite clear that many materials believed to be man-made pollutants, such as chloroform, chlorinated acetic acids, chlorinated phenols, polychlorinated dibenzodioxins and dibenzodifurans, are also produced naturally, some contributing significantly to the overall global environmental burden, having done so over geobiological time. Nothing illustrates this paradox more than the fact that the widespread production of chlorinated anisyl derivatives, such as **8**, by several species of fungi,[45] common in woodland, may yield biomass containing as much as 1% of mycelium dry weight as organically bound halogen, such that it would require labelling as hazardous waste if produced by industry.[46] All this being said, exposure to harmful amounts of a compound does not become acceptable because of its natural origin.



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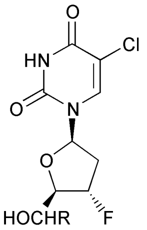

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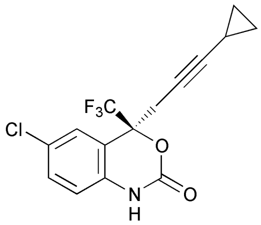

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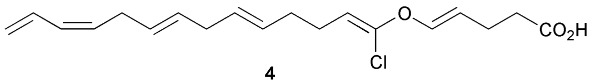

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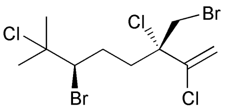

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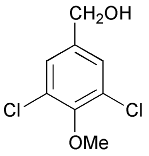

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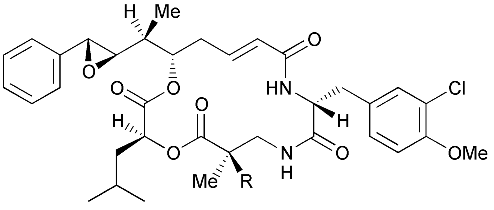

6 R = H
7 R = Me

As increasing numbers of chemicals present in the environment are shown to be produced naturally, studies of suggested pollution events will need to test whether natural sources of the chemical of concern are possible and whether the concentrations present pose significant risk. The natural 'background' concentrations of the material may then be a more appropriate base-line or reference point to which any remediation or control measure should be targeted. This is particularly relevant for the organohalogen compounds, for which Gribble[16] has documented over 3350 examples from marine and terrestrial organisms, including nearly 2000 which contain chlorine, with the latter widely but erroneously perceived to be entirely anthropogenic. Such is the quantity, variety and ubiquity of organohalogen compounds containing chlorine found to occur naturally that it now cannot automatically be assumed, as has been the case hitherto, that an organochlorine (or organobromine) compound found in the environment has an anthropogenic origin. The possibility of its arising from natural processes must be addressed.

The ubiquity of chloride ion and its essentiality to all life is established and incontrovertible (notwithstanding the on-going controversy about the acceptable amount of common salt in our diet[47]). This is most potently illustrated by the role of chloride ion as an essential co-factor in the photosynthetic production of oxygen.[48,49]

Bearing in mind that the primary production of biomass in the seas and oceans is of the order of 10^{11} tons (dry-weight) per year[50] in the presence of sodium chloride (at concentrations of *ca*. 3–4% by weight; total weight of salt in the seas and oceans *ca*. 10^{16} tons[51]), more remarkable might be the assertion that no organochlorine compounds are produced naturally in the marine environment.

It is over 20 years since Lovelock, having detected[52,53] chloromethane in unpolluted marine air, proposed its role as a natural regulator of stratospheric ozone. More recently, it has been suggested that chloromethane, a mutagen, may have played a role in evolution.[54] In the very limited number of instances in which their role has been investigated, natural chloroorganics are believed to have identifiable physiological functions which benefit the organisms that produce them. The further investigation of their role represents an important area of future research.

Such are the lifetimes of these and other haloorganics in the environment, that estimates of their present environmental concentrations suggest that natural mechanisms must also exist to transform and degrade them. Much research has been undertaken primarily to investigate the biotransformation, fate and natural destruction of organochlorine pollutants. Because of the ancient origin of many organochlorine compounds, it is reasonable to suggest that there is also a widespread and ancient capacity to break down organohalogens of all types, both naturally occurring and man-made, with such processes making up part of a geobiochemical cycle. The ultimate destruction of the haloorganic to release halide ion, water and carbon dioxide would thereby close the cycle.

In seeking better understanding of the processes of formation, transport, transformation and destruction of natural organochlorines, further research, such as the recently published global inventory of emissions of reactive chlorine-containing compounds to the atmosphere,[55–62] should provide additional evidence for, and a more quantitative description of, the natural cycles involving chlorine, analogous to the well established geochemical and biogeochemical cycles,[63–65] for oxygen,[66] sulfur,[67,68] phosphorus,[69] nitrogen[70] and carbon.[71]

Such a cycle would define and quantify the sources, sinks, reservoirs, fluxes, budgets, abundances and distributions, speciation, forms and functions for critical inorganic and organic compounds of chlorine in and between the various compartments of the earth (rock, soil, freshwater (and glaciers) and saltwater (and ice caps) and the atmosphere) and the life-forms which inhabit them.

To enhance awareness of the existence of global cycles for chlorine, this review surveys what is known of the inorganic and organic chemistry of chlorine relevant to environmental processes and also highlights some areas for further study for their better foundation.

2. Chlorine: the element, its origins, forms, distribution and cycles

Chlorine† exists predominantly in nature as chloride ion, a trace component of all the earth's geological compartments other than the oceans, its primary sink.[72] The reactivity of molecular chlorine prevents the element's accumulation, though the importance of chlorine atoms in tropospheric as well as stratospheric chemistry is increasingly recognised (see Section 2.5). Considering its essentiality to life (for example, as an obligatory co-factor in photosynthesis (see Section 2.6)), it is surprising that the distributions and fluxes of compounds of chlorine are not better understood. It is also surprising that chlorine's ubiquity and biological and biochemical importance has not led to a wider awareness of its natural organic chemistry, discussed in Section 3.

While aspects of the geochemical cycles for inorganic chlorine as chloride ion have been extensively described (see for instance ref. 51), important questions remain, particularly concerning the role of chlorine in the atmosphere, as HCl, atomic chlorine or inorganic compounds of its higher formal oxidations states, such as HOCl, $ClNO_2$, ClO_2, which, because of their high reactivity, pose much greater experimental and analytical challenges in their detection and quantification.[73] The biogeochemical cycles for chlorine, both inorganic and organic, have not been studied in the same depth as for those of other elements. However, the recent Reactive Chlorine Emissions Inventory study[55–62] has made an important step by providing global estimates, apportioned to a 2.8 × 2.8° longitudinal × latitudinal grid, of the sources to atmosphere of HCl and $ClNO_2$, as well as of selected volatile organic species (on the 64 800 1° × 1° gridded elements of the earth's surface), *viz.* chloromethane, (see also ref. 74) dichloromethane, chloroform, (see also ref. 75) methyl chloroform, trichloroethylene and perchloroethylene from anthropogenic and natural sources, including oceanic and terrestrial biogenic formation, biomass burning and sea-salt aerosol.

Relevant topics in the inorganic geochemistry, marine and tropospheric chemistry of chlorine will be surveyed in the following section, in preparation for later sections dealing with the organic, biochemical and biogeochemical role of chlorine. The latter will include relevant aspects of the organic chemistry and biochemistry of chlorine in the hydrosphere, atmosphere, lithosphere and biosphere.

2.1 Chlorine: origins and abundance

Chlorine (from χλωρος, 'chloros', meaning yellowish-green) is a member of the halogen (salt making) family, so named by Humphrey Davy in 1811 because, at that time, chlorine was unique in its ability to combine with metals directly to give salts.

As with all elements, the overall abundance of chlorine in the universe is governed by its formation and transformation in the process of nucleosynthesis in stars.[76,77] The proportion of chlorine in interstellar gas and dust has been estimated from the analysis of meteorites.[78,79] Early analyses have shown the presence of 19 Cl atoms per 10 000 Si atoms[78] and, more recently, 52 Cl atoms per 10 000 Si atoms.[79] Given that silicon is 15% by weight of the earth,[80] which itself weighs 5 980 × 10^{18} t,[63] it is thus possible to estimate the chlorine content of the earth's interior to be between 2 and 6 × 10^{18} t. The more recent

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† The term 'chlorine' will be generally used to refer to the 17th element of the periodic table in all its forms, organic and inorganic. Except where the context makes this unnecessary, dichlorine itself will be described as molecular or elemental chlorine. Chloride will be confined to inorganic chlorine in its −1 oxidation state. Compounds of organic carbon containing covalently bound chlorine will be referred to generally as organochlorine compounds.

estimate from Anders and Ebihara[79] places chlorine 19th in the list of overall elemental abundance. Thus, while chlorine is a trace element, except in the hydrosphere and in salt deposits, the overall amounts present in the earth are still massive.

Standard texts on geochemistry and environmental chemistry, including later editions, for example, refs. 81–84, ignore totally or focus little on the geochemical or biogeochemical cycles of chlorine, except in relation to the role of chlorine in the catalysis of ozone decomposition in the stratosphere. However, excellent recent reviews on chlorine geochemistry have appeared from Graedel and Keene[51,73] and on chlorine chemistry in soil by Öberg[85] to which readers are directed for more detailed accounts of what is currently known.

The earth may be divided into a number of geological compartments that make up the core, mantle and crust. The crust comprises those sub-compartments of most importance to a consideration of man's environment and cohabiting life-forms and which are the prime focus of this review, *viz.* the atmosphere, hydrosphere, lithosphere, pedosphere (the soil, characterised by the presence of material in all three phases and including an intimate mixture of living and dead organic matter) and biosphere. Some writers[82] have added the 'anthrosphere' to define a differentiated compartment dominated by man's activities.

Over geological time, all components migrate within and between geological compartments and are transported and transformed, giving rise to global cycles and to associated 'endogenic' and 'exogenic' sub-cycles. Endogenic sub-cycles involve transport of non-volatile elements *via* the magma and igneous, sedimentary and metamorphic rocks. Exogenic sub-cycles involve volatile and water-soluble elements in the hydrosphere, atmosphere and biosphere. These are represented in Fig. 1, 2[63] and 3.[85]

Some of the physical, chemical and biochemical processes involving compounds of hydrogen, carbon, oxygen, sulfur and nitrogen (including H_2O, $CO_2/[CO_3]^{2-}$, CH_4, $NO_2/[NO_3]^{-}$, $[SO_4]^{2-}$) occurring in and between these compartments have been revealed from a range of geochemical studies including those on the fractionation of natural isotopes. Developments in sampling and analytical techniques used in these approaches are now permitting such studies on the natural stable isotopes of chlorine, ^{35}Cl and ^{37}Cl[63,86,87] and to a lesser extent on ^{36}Cl formed naturally by nuclear reactions involving atmospheric argon and present also as a consequence of atmospheric nuclear weapons tests.[88] The application of these techniques to attempt to distinguish natural and anthropogenic organochlorine compounds is dealt with in Section 7.

2.2 Chlorides and the hydrosphere

Tables 1 and 2 and Fig. 4, taken from the useful summary prepared by Graedel and Keene,[51] list the major global reservoirs of chlorine and estimates of the flows between them.

Chlorine is the 20th most abundant element in crustal rock,[89] which Graedel and Keene[51] estimate to contain 60 × 10^{15} t. Because of their aqueous solubility, inorganic chloride salts enter the hydrosphere[90] and, by various processes, chloride is distributed between the hydrosphere's sub-compartments coupled by the hydrological cycle, *viz.*, the oceans[50,91–94] (97% of the hydrosphere), ice sheets and glaciers (2%), deep (0.4%) and shallow (0.3%) groundwater, lakes (0.01%), soil moisture (0.005%), rivers (0.0001%) and the atmosphere, which contains a further 0.001% as water vapour. Estimates of some of the

Table 1 Chlorine content of earth's reservoirs[51]

Reservoir	Chlorine content (10^6 t)
Mantle	22 × 10^{12}
Crust	60 × 10^{9}
Oceans	26 × 10^{9}
Pedosphere	24 × 10^{3}
Freshwater	320 × 10^{3}
Cryosphere	0.5 × 10^{-3}
Troposphere	5.3
Stratosphere	0.4

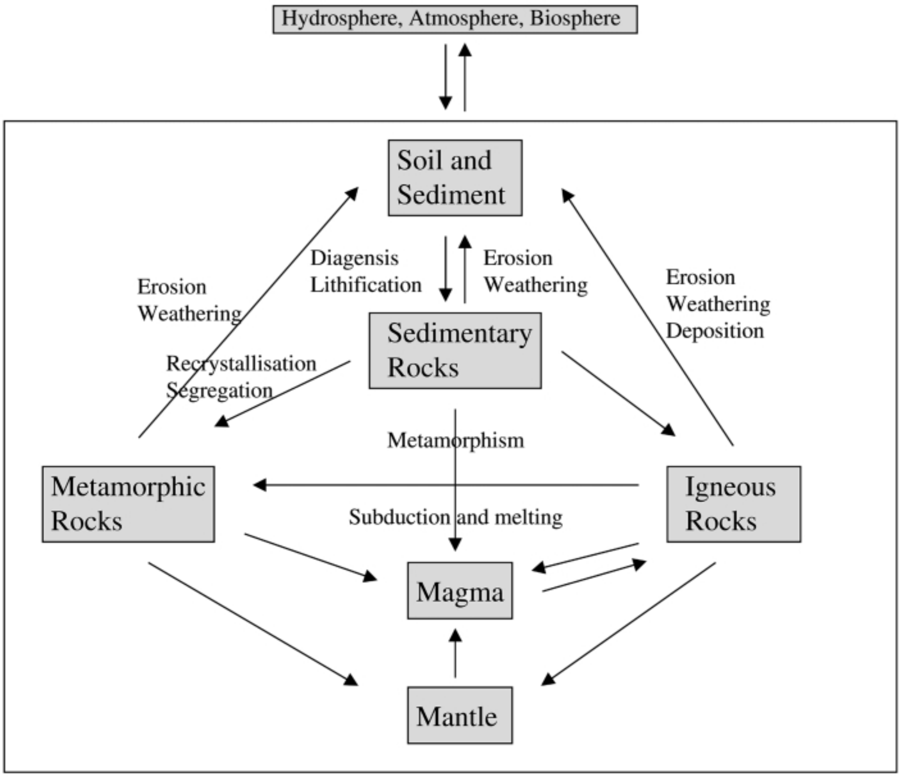


Fig. 1 Endogenic cycles connecting the principal reservoirs in the earth's interior. After Faure,[63] reproduced with permission.

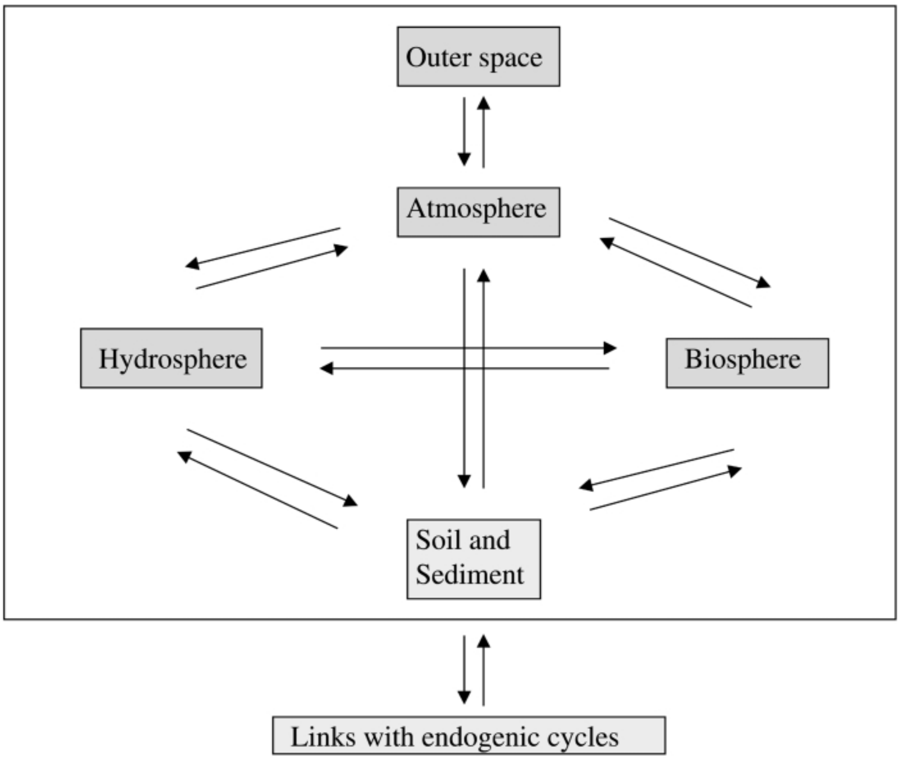


Fig. 2 The main exogenic cycles and associated reservoirs at the earth's surface. After Faure,[63] reproduced with permission.

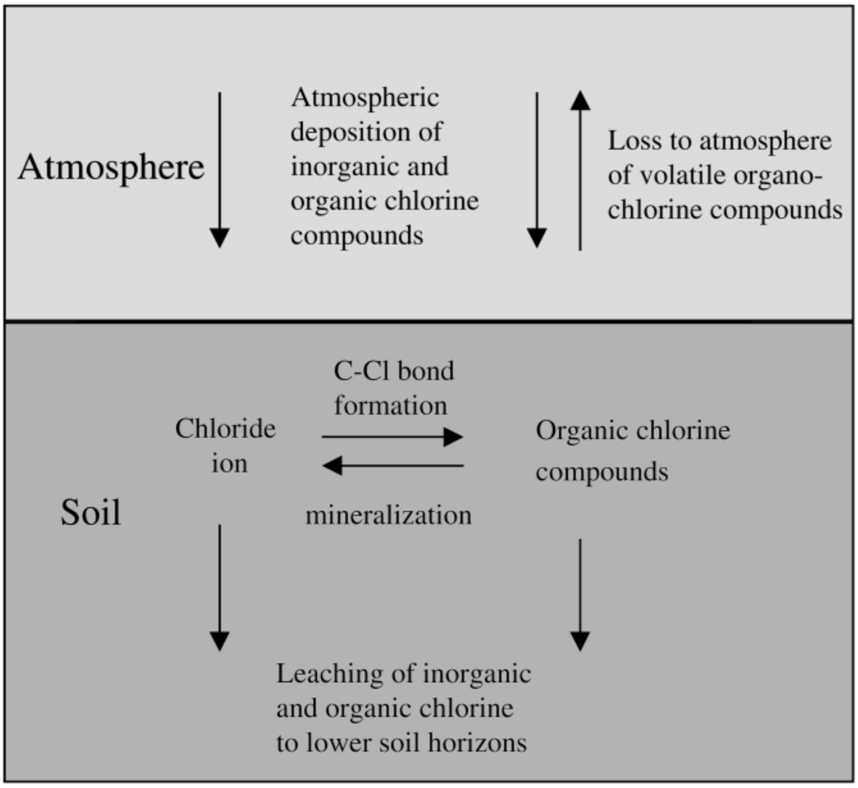


Fig. 3 Transport, transformation and storage of chloride and chloroorganic compounds in soil. After Oberg,[85] reproduced with permission.

fluxes of chlorine between these compartments have also been collected by Graedel and Keene.[51] The chloride balance in soils has been reviewed by Öberg.[85]

Dissolution of chloride in water, a consequence of the chemical and physical weathering of igneous, sedimentary and metamorphic rocks in contact with water, and subsequent riverine transport, has led to the enrichment of sea water compared with average river water by a factor of *ca.* 2500. Meybeck has estimated a net flux of 3.3×10^{12} mol Cl per year in a total discharge of 37.4×10^{15} L of river water per year.[95]

Elements, such as chlorine (and bromine), which are present as their anions at high concentrations in sea water compared with river water (that is, have high enrichment factors) are believed to be relatively unreactive compared with elements and species with low enrichment factors, such as sulfur or iodine. The latter are thought to be relatively rapidly removed from seawater by various processes, including deposition in sedi-

Table 2 Estimated flux (10^6 t per year) of chlorine between reservoirs[51]

Inter-reservoir transfer		Flux
Mantle to troposphere		2
Pedosphere to troposphere	*Mineral aerosol*	15
	Biomass burning	3
	Bioproduced	0.5
Crust to freshwater		175
Pedosphere to freshwater	*Precipitation passthrough*	34
	Evaporite beds	11
Freshwater to oceans		220
Oceans to troposphere	*Seasalt injection*	6000
	HCl from seasalt (a proportion of seasalt injection flux)	25
	Magma intrusion	4
	Bioproduced	2
Troposphere to surface	*Oceans*	5990
	Pedosphere	34
	Cryosphere	6
Troposphere to stratosphere		0.03
Stratosphere to troposphere		0.03
Oceans to crust		17

ments (which leads ultimately to diagenesis, *i.e.*, re-entry into the rock-forming cycle) or by other physical, chemical or biological processes. An estimate of *ca*. 10^8 years has been made[50] for the mean ocean residence time of chloride, providing a measure of the apparent timescale of geological and geochemical processes driving some of the cycles involving chloride.

This apparent relative global unreactivity of chloride may have been seen as indicating the complete lack of, or the relative unimportance of, processes driving other geochemical or geobiological cycles involving chlorine. However, evidence collected in other sections of this review reinforces the view that an organic cycle for chlorine should now be recognised, in addition to its inorganic cycle, and its important characteristics should be better defined.

The oceans, the main reservoir for chloride in the hydrosphere, contain an estimated 26×10^{15} t of chloride.[51] While it is generally thought[50] that the average concentration of chloride in sea-water has remained roughly constant over the past 600 million years, the variation of the salinity of the oceans over geological time is still a matter of debate.[96] It is has also been argued[97] that there is more chloride (and other elements such as sodium, magnesium and potassium) in the oceans than can be accounted for by weathering of igneous rocks in the crust, a conclusion that relies on values of the balance ratio for chloride [balance ratio = (the ratio of the average concentration in sedimentary rocks + oceans)/(the average concentration in crustal igneous rocks)]. Most elements have balance ratios[98] in the range 0.8 to 1.3, whereas, for chlorine, this ratio is *ca*. 150. Schilling and co-workers have proposed[99] that chlorine from the mantle is continuously transferred into the oceans by volcanic processes at the mid-ocean ridge and other hot-spots. Transfers of chlorine between the mantle and surface reservoirs have also been discussed in terms of the effects of plate tectonic processes.[100]

Were there to be a steady state for chloride inputs to and outputs from the oceans, then, it was believed, river-borne inputs would be balanced by outputs to pore water buried with sediment, ion-exchange, diagenesis (the movement of sediment into the mantle (see ref. 100)) and chemical and biochemical processes. Only the first of these was thought to be important for chloride. With an input to output ratio for chloride estimated to be *ca*. 10, there appears to be more entering the oceans than leaving them than could be accounted for by episodic marine evaporation that has given rise to the enormous sodium chloride deposits around the world. It now also appears that sea water may enter the earth's crust along the crest of the volcanic mid-ocean ridges to reappear as hot springs and 'smokers', the latter at temperatures of *ca*. 350 °C. (See, for instance, refs. 99–102.)

2.3 Sea-salt aerosol

While it is possible that the salinity of the seas is, in fact, increasing with time, significant losses of salt from the sea to the atmosphere are also believed to arise in the form of marine or

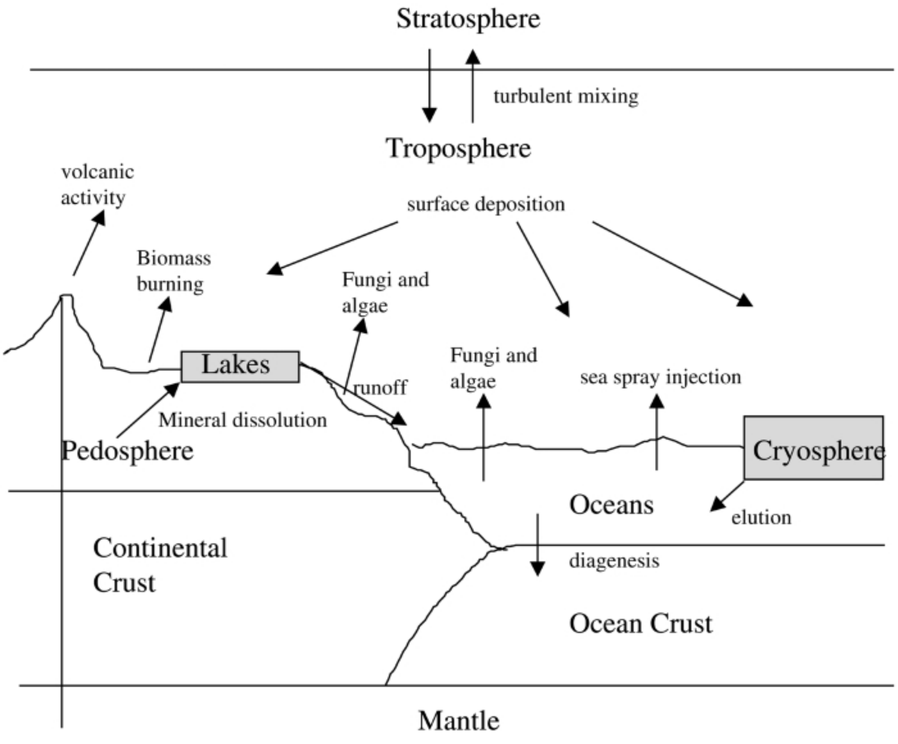


Fig. 4 The earth's major reservoirs of chlorine and natural processes which transfer chlorine between reservoirs (see Table 1 for reservoir sizes and Table 2 for fluxes). After Graedel and Keene,[51] reproduced with permission.

sea-salt aerosol (concentrated droplets containing a variety of ionized salts (plus smaller quantities of organic species) formed by turbulent wind and associated wave action at the surface of the oceans[103]) and its redeposition over the continents. The riverine input to the oceans must, therefore, include some redeposited chloride in addition to that arising from dissolution by weathering.

Data summarised by Graedel and Keene suggest that sea-salt aerosol injects *ca.* 6×10^9 t per year of salt into the marine boundary layer (that is, the 1 000 m of the troposphere above the ocean's surface). Most of the larger aerosol particles are deposited back into the sea or washed out of the atmosphere in marine precipitation, which contains on average 100–200 μmol $Cl^- L^{-1}$. Some particles are small enough to be transported over land where similar processes of dry deposition or dissolution and precipitation can transfer chloride onto the continents. The higher chloride content of vegetable matter near coasts is consistent with this. Continental rain contains up to 15 μmol $Cl^- L^{-1}$, with *ca.* 20×10^6 t Cl per year of an estimated total of 34×10^6 t Cl per year deposited on land masses arising from precipitation. More recent estimates,[58] computed with a dynamic sea-salt aerosol model coupled with a series of relevant chemical processes described in more detail below, suggest that sea-salt aerosol injects 2.8×10^9 t NaCl per year (1.8×10^9 t Cl per year) into the marine boundary layer, lower than previous estimates.

The importance of chlorine as a component of air over the oceans was first recognised by Smith in 1872 who also suggested the formation of HCl by acid displacement from sea-salt aerosol by atmospheric sulfuric acid.[104] The geochemical significance of sea-salt deposition as the origin of most of the chloride in river water was also recognised in 1877 by the Hungarian geologist, Posephny.[105,106] (The role played by sea-salt particles in the condensation of clouds was also recognised earlier this century by Kohler.) The wider role of atmosphere–ocean aerosol exchange in the biogeochemical cycling of carbon, nitrogen, sulfur and phosphorus has been reviewed by Duce.[107]

The suggestion that sea salt may be the source of both atmospheric HCl as well as oxidizing chlorine-containing species has been the subject of speculation in many early studies. This early work has been reviewed by Altshuller[108] and Eriksson.[105,106] First Smith,[104] then Eriksson[105,106] and Robbins *et al.*,[109] proposed that HCl is released from sea-salt particles as a consequence of pH reduction (sea-salt aerosol from unpolluted regions is alkaline, becoming acidic in polluted marine air[110]) associated with the dissolution of the oxides of sulfur and nitrogen or their associated acids [eqns. (1) and (2)], which are atmospheric components with significant anthropogenic sources.

$$HNO_3\,(g) + NaCl\,(s) = HCl\,(g) + NaNO_3\,(s) \qquad (1)$$

$$H_2SO_4\,(g) + 2\,NaCl\,(s) = 2\,HCl\,(g) + Na_2SO_4\,(s) \qquad (2)$$

Nikonova and Epshtein[111] showed experimentally that solid NaCl (and, by inference, salt in sea-salt aerosol) could react with nitric acid to produce sodium nitrate, NOCl, molecular chlorine and water. This process was judged to be of little importance, though, following work by Cadle and Robbins,[112] Eriksson[106] accepted that HNO_3 could displace HCl in a manner similar to H_2SO_4. In addition, Valach[113] believed that the amounts of HCl found in the atmosphere could not be accounted for by the process of H_2SO_4 displacement and suggested volcanoes as an alternative source, a suggestion refuted by Duce.[114]

It was Cauer who, in 1938[115] and again in 1951,[116] first proposed that gaseous chlorine as Cl_2 could be released from sea-salt particles. He proposed ozone as the oxidant for chloride, though Eriksson[106] argued that this reaction was probably too slow to account for the observed amounts of chlorine in the atmosphere. Using data from Yeatts and Taube,[117] Eriksson[105,106] estimated a half-life for the conversion of chloride to hypochlorite ion (the precursor for molecular chlorine formation) as $> 10^3$ years in sea droplets, requiring, in Eriksson's view, a five orders of magnitude acceleration of reaction in sea-salt particles, which he judged unlikely. However, this would very much depend on sea-salt pH, the calculation of which is itself dependent on the Henry's Law constant for HCl, which may vary widely. More recent work on halogen displacement from sea-salt aerosol is discussed below.

2.4 Hydrogen chloride and the atmosphere

The early work of Junge[118] suggested that the only gaseous form of chlorine was HCl and derived products, such as ammonium chloride, the HCl arising from volcanic sources and sea-salt aerosol. Junge concluded that elemental chlorine could not be formed. See, however, Section 2.5.

The main sources of atmospheric HCl are anthropogenic (such as from coal burning and waste combustion), natural (from volcanoes and sea-salt aerosol), a combination of the two (such as from biomass burning) and indirectly anthropogenic (from sea-salt aerosol by reaction with the anthropogenic component of the acids, HNO_3 and H_2SO_4). The latest global estimate[60] suggests that $(4.6 \pm 4.3) \times 10^6$ t HCl arose in 1990 from the combustion of coal (the chloride content of coal varies between tens of parts per million (ppm) to $> 1\%$). In the same study, an estimated $(2 \pm 1.9) \times 10^6$ t HCl was thought to arise from the burning of municipal and domestic waste. Biomass burning[62] gives rise to volatile inorganic chlorine (predominantly HCl) and particulate chlorine amounting to 6.3 (4.4–8.3) $\times 10^6$ t, with much uncertainty associated with variation in agricultural practice, fuel and vegetation type and its chlorine content, combustion conditions, seasonal factors and plume chemistry. It has been estimated[119] that *ca.* 90% of biomass burning is of non-industrial anthropogenic origin (savanna fires and wood and charcoal burning being the major contributors[62]) with wholly natural processes, such as fires caused by lightning strikes and volcanic lava flows, being relatively unimportant. Graedel and Keene[73] estimate annual emissions of HCl from volcanoes to be *ca.* 2×10^6 t.

Because of its water solubility, HCl is readily removed from the atmosphere in precipitation and has an associated atmospheric lifetime of *ca.* 1.5 days.[58,60] Some HCl escapes from the upper atmosphere into the stratosphere, sufficient to cause slight increases in the stratospheric global chlorine burden particularly following substantial volcanic eruptions. For instance, the Mount Pinatubo eruption of June 1991 released an estimated 4.5 $\times 10^6$ t of HCl,[120] most of which was scavenged in condensed water in the plume produced by the eruption.[121] The changes in the concentration of HCl in the lower stratosphere which followed the Mt. Pinatubo eruption have been monitored.[122] (It is worth noting here that the injection of aerosols from the Mt. Pinatubo eruption has been associated with increased chlorine dioxide formation and with the depth and area of the Antarctic ozone hole in 1992.[123])

10–300 parts per trillion by volume (1 part in 10^{12}; pptv) HCl is commonly found in the atmosphere at the surface of remote ocean regions, with variations over land and coastal areas. HCl concentrations also have been found to vary with time of day, with, in urban areas, a maximum in the afternoon. This peak may possibly be associated with an earlier peak in HNO_3, suggesting that sea salt may be the dominant source of this HCl, *via* an acid displacement process.[73]

Sea-salt aerosol is thought to be the largest atmospheric source of HCl, though flux estimates vary. The variation in the analyses of chloride and other ions in sea-salt aerosol, compared with the ion content of the sea from which the aerosol arose, consistently points to a variable chloride ion deficit, associated with sea-salt particle size, its history, and the local environment. The greatest chloride ion deficits are seen in particles exposed to the most heavily polluted air masses in the northern hemisphere. Changes in the Cl:S and Cl:N ratios point to displacement processes, involving atmospheric sulfuric and nitric acids, which result in the removal of chlorine as HCl from sea-salt aerosol, according to processes shown in eqns. (1) and (2).

This has been verified by Keene *et. al.*[124] and a mechanism proposed by Laux *et al.*[125] Direct observation of the replacement of chloride by nitrate on single tropospheric sea-salt particles has been described by Prather *et al.*[126] using aerosol time-of-flight mass spectrometry. While estimates are currently uncertain, Graedel and Keene,[73] using two different methods, estimated the HCl flux from this source to be *ca.* (37–73) $\times$ 10^6 t C per year or (50–85) $\times$ 10^6 t Cl per year. However, more recently, an estimate (net of interparticle exchange) smaller by a factor of about 10, 7.6 $\times$ 10^6 t Cl per year, has resulted from studies[58] which modelled sea-salt production and some aspects of sea-salt chemistry in the marine boundary layer (including reactions involving gas phase HNO_3, N_2O_5, NH_3, SO_2, H_2SO_4, H_2O_2 and O_3). The dependence of HCl flux on sea-salt particle size, month (greatest in February, least in July) and location (varying from 1 to 300 mg Cl m^{-2} per year) was also reported. The model studies also suggest that significant fractions of HCl volatilized by acid displacement processes may be scavenged by aerosol, resulting in a net transfer of acid from small to large and from old to young aerosol particles.

2.5 ‘Reactive’ chlorine in the atmosphere

An understanding of natural atmospheric chemistry is important because many organic materials, some chlorine-containing, degrade and mineralise in the troposphere or stratosphere, with concomitant significant direct and indirect environmental effects, local, regional or global. It is important for the minimisation of any deleterious impact arising from an anthropogenic input of both chlorine-free as well as chlorine-containing materials that such chemistry is understood.

Work reviewed by Cicerone[127] and by Ryan and Mukherjee[128] has highlighted the impact on stratospheric photochemistry of long-lived chlorine-containing materials produced and emitted anthropogenically. Chlorine atoms, oxychloro radicals and chlorine nitrate (derivatives of so-called ‘reactive’ chlorine) are now known to be important (and detectable) intermediates in the stratosphere[129–132] with chlorine atoms and $ClO^\bullet$ involved directly in various cycles that lead to the catalytic decomposition of stratospheric ozone.[133]

Recently, the role of shorter-lived compounds (particularly of bromine, such as bromoform (global flux 0.3 $\times$ 10^6 t per year; tropical tropospheric lifetime 2–3 weeks) and dibromomethane (global flux 0.05 $\times$ 10^6 t per year; tropical tropospheric lifetime 2–3 months), though also of chlorine) has been included[134] in stratospheric ozone models to improve treatment of ozone depletion in the lower mid-latitude stratosphere. Indeed, a significant proportion (*ca.* 15–20% [135,136]) of stratospheric ozone destruction catalyzed by chlorine arises from atomic chlorine formed photolytically from an everpresent background level of chloromethane.

Much less attention has been devoted to the tropospheric chemistry of reactive chlorine, though developments have been reviewed by Graedel and Keene,[73,124] Keene[137] and very recently by DeHaan *et al.*[138] It is the result of careful work done over the past decade that the assumption that the sole (or chemically most important) tropospheric form of volatile inorganic chlorine is HCl has been questioned once more and the suspected role of other inorganic chlorine-containing species[127] confirmed. Pszenny *et al.*[139] Impey *et al.*[140,141] and Spicer *et al.*[14] have recently detected oxidizing chlorine-containing species in the marine atmosphere. While the precise chemical nature, abundance and distribution of these additional species remain to be unequivocally established, there is no doubt that they are either elemental chlorine, derivatives of chlorine in a positive oxidation state, such as HOCl, $ClNO_2$ or $ClNO_3$, or other derivatives, such as BrCl, from which atomic chlorine may be generated photochemically.

The first evidence of inorganic reactive-chlorine-containing species was reported by Pszenny *et al.*[139] who proposed that, on average, 100–150 pptv of such species may be present in surface marine air, and, though the pattern of formation was different from that for HCl, sea salt was the source.

Because of the very considerable experimental and analytical challenges involved in collecting and analysing sea-salt aerosol, it is not surprising that there have been a number of laboratory studies which sought to mimic, with varying degrees of success, the interactions of synthetic sea-salt aerosol (or some surrogate) with possible oxidising tropospheric components (HNO_3, N_2O_5, NO_2, O_3, HOBr) and to study the effect of atmospheric variables such as temperature, humidity and light. Early investigations have already been mentioned.[105,106,111,115,116] Attention is increasingly being focused on tropospheric ozone destruction in the Arctic, particularly during the polar sunrise, where processes involving bromine are thought to be more important than those involving chlorine.[141–149] Iodine chemistry may also play a role.[150–152]

The need to understand these critical heterogeneous processes in the atmosphere has stimulated many fundamental studies. A selection of very recent reports includes the laboratory study of the dynamics of reactions involving chlorine and bromine-containing or -producing atmospheric components such as HOBr,[153] N_2O_5, NO_3 and HNO_3,[154–159] and XNO_2, X = Cl, Br,[160] with solid alkali metal halides, of $ClONO_2$, HCl and HOCl,[161–165] $BrONO_2$,[143] $ClONO_2$[166,167] or NO_3,[158] on water ice, of XNO_2[168,169] or HOBr[144] on salt solution droplets and of $ClONO_2$ on sulfuric acid aerosol.[170–172] Physical chemical studies of HOBr solubility in sulfuric acid (and of its reaction with HCl to give BrCl),[173] of Cl_2 formation from aqueous HCl and HNO_3,[174] eqn. (3), and of BrCl aqueous solution–vapour equilibria[175] have been undertaken because of their relevance to atmospheric processes on and in aerosol droplets (of whatever type or origin[176]).

$$4\ H^+\ (aq) + NO_3^-\ (aq) + 3\ Cl^-\ (aq) \ = \ NOCl\ (aq) + Cl_2\ (aq) + 2\ H_2O\ (l) \qquad (3)$$

Of particular relevance is the work of Finlayson-Pitts *et al.*,[177–182] Behnke and Zetzsch,[183–189] Vogt *et al.*[145,151] Sander and Crutzen[190] and Mozurkevich[191] who have examined processes exemplifed by eqns. (4)–(8) involving simulated sea-salt aerosol.

$$N_2O_5\ (g) + NaCl\ (s) \ = \ ClNO_2\ (g) + NaNO_3\ (s) \qquad (4a)$$

$$N_2O_5\ (g) + Cl^-\ (aq) \ = \ ClNO_2\ (g) + NO_3^-\ (aq) \qquad (4b)$$

$$2\ NO_2\ (g) + NaCl\ (s) \ = \ NOCl\ (g) + NaNO_3\ (s) \qquad (5)$$

$$O_3 + 2\ NaCl(s) + H_2O \ = \ Cl_2\ (g) + 2\ NaOH\ (s) + O_2\ (g) \qquad (6)$$

$$ClNO_2 + H_2O \ = \ HOCl + HNO_2 \qquad (7)$$

$$HOBr + Cl^- + H^+ \ = \ BrCl + H_2O \qquad (8)$$

In 1974, Schroeder and Urone[192] first reported that nitrosyl chloride and sodium nitrate could be formed in the heterogeneous reaction of NO_2 with crystalline sodium chloride, eqn. (5). Recent work by Weis and Ewing[193] has established the stoichiometry for this process *in situ* by exposing particles produced by atomizing aqueous synthetic sea-salt solutions to 1–3 mbar NO_2 at low (9–30%) relative humidity (RH). Finlayson-Pitts[181] showed that this reaction occurs down to ppm levels of NO_2, suggesting that it should be considered alongside reactions of HNO_3 and N_2O_5. However, it is N_2O_5 which is thought to be the most significant source of $ClNO_2$

formed *via* a night-time reaction with sea-salt aerosol. N_2O_5 may be formed in the atmosphere from the reaction of NO_2 and ozone, giving NO_3 which reacts further with NO_2. Laboratory measures of the reaction probability associated with eqn. (4a) decline with increasing humidity, but yields are still *ca.* 30% even at RH of 92%.[187,188] Reactions involving ozone have also been studied,[146,180,184–186,189,194] including a very recent laboratory investigation[195] of the oxidation of mixed solutions of NaBr, NaCl and HNO_3 in which ozone reacts with bromide according to a variant of eqn. (6), *viz.* eqn. (6a), followed by eqn. (8).

$$O_3 + H^+ + Br^- = O_2 + HOBr \qquad (6a)$$

The reaction of ozone, hydrocarbons and sodium chloride aerosol (in smog chamber experiments[189]) is found to require the presence of bromide in the aerosol for activation.

Vogt *et al.*[145] have proposed an autocatalytic role for bromide in the formation of 'positive' chlorine-containing species in the remote and unpolluted marine boundary layer. Hypobromous acid, formed by bromide oxidation, may itself be scavenged by chloride ion in sea-salt aerosol to generate bromine chloride according to eqn. (8) which may be subsequently photolysed, eqn. (9). Reactive bromine is also reportedly released from the Dead Sea, though by processes occuring on the surface of salt pans, rather than as a consequence of reactions on aerosols.[147] Very recently, Vogt *et al.*[151] have suggested from modelling studies that iodine (originating from the atmospheric degradation of biogenic alkyl iodides, particularly CH_2I_2, CH_2ClI, CH_3I, C_2H_5I and C_3H_7I) may further accelerate bromine and chlorine release from sea-salt aerosol by processes such as eqns. (8a) and (8b).

$$BrCl + h\nu = Br^\bullet + Cl^\bullet \qquad (9)$$

$$HOI + Cl^- + H^+ = ICl + H_2O \qquad (8a)$$

$$HOI + Br^- + H^+ = IBr + H_2O \qquad (8b)$$

Species such as IO[196] (also recently detected at lower latitudes[152]) and BrO[147,196] (see ref. 197 for a recent study) have been estimated spectroscopically in the polar marine boundary layer. Modelling suggests such species have a profound influence on ozone-loss processes.

Only very poor estimates for the overall production rates of reactive chlorine species are currently available, spanning the range < 100–800 × 10^6 t Cl per year.[73] There are also few reliable estimates for the production rates of individual species. Erickson *et al.* have suggested from recent modelling studies[58] that *ca.* 60 × 10^3 t Cl per year arise in the form of $ClNO_2$. There is thus a major need for further research to better understand these processes, fluxes and their implications.

Species such as BrCl, Cl_2, $ClNO_2$ and HOCl may photolyse to generate chlorine atoms (eqns. (9)–12)) the most likely fate of which is to react, as in eqn. (13), with C–H groups by atom abstraction to form HCl and organic radicals which may react further with oxygen *via* well known reaction pathways. The potential for the HCl produced to be scavenged by undersaturated sea salt would complete a cycle proposed by Keene *et al.*[110,124] and modelled by Erickson *et al.*[58] Other possible fates of such chlorine-containing species are discussed below.

$$Cl_2 + h\nu = 2\,Cl^\bullet \qquad (10)$$

$$ClNO_2 + h\nu = Cl^\bullet + NO_2 \qquad (11)$$

$$HOCl + h\nu = HO^\bullet + Cl^\bullet \qquad (12)$$

$$Cl^\bullet + R\text{-}H = HCl + R^\bullet \qquad (13)$$

In addition to chlorine-atom formation from eqns. (9)–(12), eqns. (14) may also be a possible source.

$$HCl + OH^\bullet = H_2O + Cl^\bullet \qquad (14)$$

These possibilities have led to a discussion of the role of chlorine atoms in atmospheric oxidation chemistry, as the hydrogen abstraction reaction by chlorine atoms (eqn. (13)) is generally faster than the corresponding process for hydroxyl radical, (eqn. (15)),[198] the principal atmospheric oxidant. For example, for R = CH_3 at 298 K, the second-order rate constant for reaction with $Cl^\bullet$ is *ca.* 15-fold larger than for the corresponding reaction with $OH^\bullet$. It is possible, therefore, that relatively small concentrations of chlorine atoms could still play a significant part in atmospheric oxidations. It is to be expected that processes involving 'reactive' chlorine will be most important in the marine boundary layer.

$$OH^\bullet + R\text{-}H = H_2O + R^\bullet \qquad (15)$$

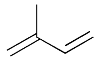
The acceptance of the importance of processes involving chlorine atoms depends crucially on estimates of the chlorine atom concentration in the atmosphere and the unequivocal detection in the unpolluted atmosphere of elemental chlorine from a natural source. It is significant, therefore, that Spicer *et al.*[14] have recently reported the direct observation of elemental chlorine at concentrations between < 10 and 150 pptv, at night-time at a North American coastal site during the flow of onshore winds from unpolluted marine sources.

Graedel and Keene[73] have brought together estimates of chlorine-atom concentrations in the marine boundary layer. These range from 10^3 atoms cm^{-3} (in the global troposphere, from models of eqn. (14)) to 10^5–10^6 atoms cm^{-3} (estimated for the North Atlantic in summer from Cl-deficits in sea-salt aerosol, assuming chlorine to be the primary species produced). Such estimates are controversial, since if the concentration is > 10^4 atoms cm^{-3}, elemental chlorine must be seen as playing an important and hitherto unacknowledged role in atmospheric chemistry of the marine boundary layer.

Indirect evidence for the role of chlorine (and other halogens) in atmospheric chemistry has been sought from field observations and modelling of ozone depletion in the Arctic troposphere[199] and from the simultaneous measurements of the concentrations of nonmethane hydrocarbons, such as ethane, propane and n-butane, in aged air masses arriving at a sampling point. Changes with time in the ratios of one hydrocarbon in an air mass to another (and plots of ln[alkane(1)]/[alkane(2)] *vs.* ln[alkane(3)]/[alkane(2)]) (assuming, amongst other things, that diluting air adds neglible additional hydrocarbon) have been simulated using kinetic data for reaction of the alkanes with hydroxyl radical. The involvement of other oxidants, such as halogen atoms, has been invoked to improve the fit between calculation and observation. Parrish *et al.*,[200] Singh *et al.*[201] and Rudolph *et al.*[202] have concluded that chlorine chemistry is not important in these processes. On the other hand, in studies of the Arctic polar sunrise in 1992 (Jobson *et al.*[203]), 1994 (Ariya *et al.*[204]) and 1995 (Ariya *et al.*[205]), chlorine atoms have been implicated in ozone depletion events and alkane chemistry after the polar sunrise (hydroxyl-radical chemistry dominating prior to the sunrise). In a recent report,[206] model-fitting of experimental data from over 1400 whole air samples collected over the southern ocean, 700 from the marine boundary layer, 300 from the free troposphere and the remainder from the buffer layer, produced estimates of average [$HO^\bullet$] of (6.1 ± 0.3) × 10^5 radicals cm^{-3} and [$Cl^\bullet$] of 720 ± 100 atoms cm^{-3}. The change in the ratio of the concentrations of a pair of reactive tropospheric organics is likely to be greater, the greater the difference in rate constants for reactions with different oxidants. On this basis, Rudolph *et al.*[207] estimated, from measurements of tropospheric ethane and tetrachloroethylene, upper limits for chlorine-atom concentrations in the Northern and Southern Hemispheres to be 1 × 10^3 and 2 × 10^3 atoms cm^{-3}, respectively, concluding that chlorine-atom induced processes were unimportant. Remeasurement of the rate constants for the reaction of tetrachloroethylene and trichloroethylene with chlorine and bromine atoms enabled Ariya *et al.*[208] to model Arctic troposphere ozone depletion episodes which yielded much higher estimates of the (daytime) concentration of bromine (10^7 atoms cm^{-3}) compared with chlorine (10^4 atoms

cm^{-3}). The basis of these studies could be confounded were significant local natural sources of trichloroethylene and tetrachloroethylene to be found, a possibility that is discussed further in Section 4.2. The variation of the concentration of ethyne during the Arctic sunrise also points to a significant role for bromine atoms. In very recent work, Ramacher *et al.*[209] propose, from hydrocarbon measurements, that free chlorine contributes only *ca.* 1% of the ozone loss during episodic tropospheric ozone depletion events which occur during the Arctic spring, with bromine atoms being the predominant cause ($>92\%$) of depletion. This further reinforces suggestions (see refs. 141–149, 204 and elsewhere) that tropospheric ozone loss in the marine boundary layer, particularly during the Arctic sunrise, is driven primarily by autocatalytic processes involving bromine. Barrie and Platt[199] and Platt and Moortgat[210] have provided brief overviews of this topic. Sunrise ozone destruction in the sub-tropical marine boundary layer has also been associated with chemical processes involving bromine.[211] Rudolph *et al.*[212] have recently employed halogen-atom concentration estimates obtained from studies of hydrocarbon losses to investigate the possible effect of bromine and chlorine chemistry on the concentration of formaldehyde in the Arctic troposphere during ozone depletion events at the polar sunrise. Recently, reductions in the $^{13}C/^{12}C$ ratio for carbon monoxide which occurred during episodes of ozone depletion during the Arctic spring have been ascribed to oxidation of methane initiated by elevated concentrations of chlorine atoms formed during these episodes.[213]

Ragains and Finlayson-Pitts[214] (and more recently Wayne and colleagues[215]) have studied the kinetics and mechanism of the gas-phase reaction of chlorine atoms and isoprene **9** (450×10^6 t of which is emitted naturally to the atmosphere each year[216]), methacrolein and methyl vinyl ketone. Product studies[217] suggest that *ca.* 15% of the reaction proceeds *via* an allylic hydrogen-atom abstraction and the remainder *via* chlorine addition to a double bond, giving compounds such as **10** whose detection in the environment (as ‘sentinel’ compounds) would provide evidence of the importance of these natural processes. An excellent precedent that the collection of such evidence may be possible arises from recent reports of the detection in ambient air of five organic nitrates derived from isoprene.[218] Mechanistic studies for the reaction of 2-methyl-3-buten-2-ol with $HO^{\bullet}$ and $Cl^{\bullet}$ have also been reported.[219]



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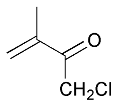

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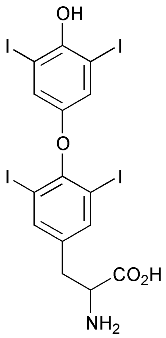

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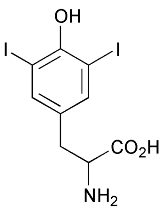

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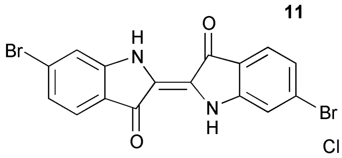

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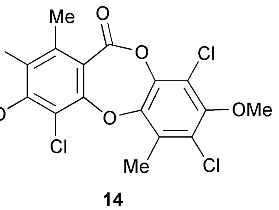

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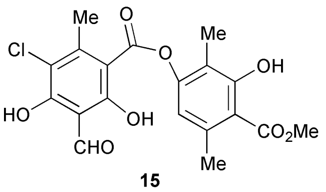

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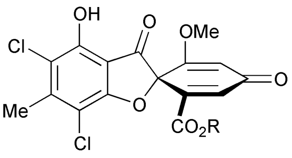
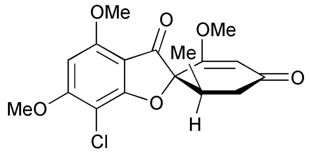


16 R = H
17 R = Me



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Chlorine photochemistry has also been proposed to account for anomalies in the oceanic sources and sinks for atmospheric dimethyl sulfide which cannot be accounted for satisfactorily by processes involving known oxidants such as hydroxyl and nitrate radicals.[220] Discussions of the atmospheric decay of dimethyl sulfide have also suggested a role for bromine chemistry.[221]

The linkage between cycles involving the halogens, iodine, bromine and chlorine has already been mentioned (and will be discussed further in Sections 5 and 7 in the light of recent work[222] on enzyme-mediated halide exchange on monohalomethanes). Japanese workers have recently described the formation of bromine from the interaction of chlorine and both synthetic and natural sea salt.[223] On the other hand, Goliff and Rowland have concluded that replacement of iodine or bromine by atomic chlorine is not important as a source of atmospheric CH_3Cl, having shown[224] experimentally that CH_3I and CH_3Br yield only 8.6 and 0.6% of CH_3Cl respectively on reaction with thermal chlorine atoms.

2.6 Chloride as an essential co-factor in photosynthesis

The oxidation of water to oxygen in photosynthesis is essential to most life on earth.[48] Two photosystems (PSI and PSII) are involved in the critical parts of the photosynthetic process. PSII, a transmembrane protein complex, catalyzes water oxidation (and the reduction of plastoquinone to plastoquinol). A photoexcited chlorophyll species, P680, loses an electron to become $P680^+$, the electron acceptor in water oxidation, which is rereduced by a manganese cluster complex.[48,225] This oxygen-evolving complex consists of a cluster at the core of which are 4 manganese ions.[226] The complex is oxidised by $P680^+$ *via* a series of five cluster oxidation states (designated S_0–S_4) with concomitant oxidation of water to oxygen, the latter released on production of S_4. Chloride ion has been found to be an essential co-factor in these processes,[48,49,226–231] with Cl^- depletion leading to a complete (though reversible) inhibition of oxygen evolution. This is thought to occur by interference with the redox chemistry of the manganese cluster. Fine and Frasch[232] show that chloride prevents the formation of hydrogen peroxide and suggest that chloride prevents access to the active site of the oxygen-evolving complex until the accumulation of the four oxidizing equivalents needed to convert water to O_2. More recently, chloride ion has been found to be necessary for the S_2–S_3 and S_3–S_0 transitions but not the S_0–S_1 or S_1–S_2 transitions.[233] The synthesis of model clusters containing the $[Mn_4O_3X]$ core, X = Cl, Br, has been reported (see for example ref. 234) which display some of the physical and chemical characteristics of the oxygen-evolving complex, though none yet replicates all the critical features.

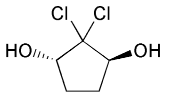
3. Organochlorine compounds: diversity, ubiquity and function

Any attempt to define an elemental cycle must seek to establish the identity, sources, sinks, distribution, reservoirs and fluxes of all materials containing the element, organic and inorganic, within and between the various geological and environmental compartments and sub-compartments, as well as providing an understanding of the processes, physical, chemical and biological, that give rise to their formation, transformation, transport, storage and destruction, and an appreciation of the consequences of their presence, and how all these phenomena change on various spatial and temporal scales. Even well studied cycles, such as those for carbon and oxygen, are far from complete.

Despite much work, the definition of a cycle for chlorine is, to say the least, at its very early stages. However, in one respect, a great deal is now known. This section summarises evidence concerning the natural formation of organic compounds containing chlorine.

3.1 History

General perceptions regarding the non-natural origins of organochlorine compounds may be contrasted with the wider recognition of natural sources of organic compounds of iodine, such as thyroxine **11** and 3,5-diodotyrosine **12**. In 1896 Dreschel reported the isolation from the gorgonian *Gorgonia cavolinii* of an organic compound with the empirical formula $C_4H_8NIO_2$, the first natural product demonstrated to contain carbon–halogen bonds.[235] The isolate was subsequently shown to be 3,5-diodotyrosine by Henze in 1907.[236,237] The isolation of the hormone thyroxine was not reported until 1915.[238] However, it is Tyrian purple, the royal purple dye of antiquity,[239,240] produced from the extracts of the Mediterranean mollusc, *Murex brandaris*, that can probably lay claim to be the first known organohalogen. The production and use of Tyrian purple was described in the first century AD by Pliny the Elder,[241] though it was not until 1909 that Friedländer established it to be the dibrominated indigo derivative **13**.[242] Diploicin **14**, a depsidone extracted from a lichen by Zopf in 1904,[243] may be considered to be the first isolated chlorine-containing metabolite, though reports of its characterisation did not appear until June 1934.[244,245] However, chloratranorin (another ubiquitous chlorinated depside isolated in 1907, also by Zopf[246]) probably qualifies as the first chemically characterised example. The characterisation of chloratranorin as 3-hydroxy-4-methoxycarbonyl-2,5-dimethylphenyl 3-chloro-5-formyl-4,6-dihydroxy-2-methylbenzoate **15** was announced by Koller and Pöpl in May 1934,[247] and described more fully shortly afterwards.[248] St. Pfau (in a paper received for publication on 30 August 1934[249]) also reported its isolation and structure at about the same time. The subsequent discoveries of erdin **16**, geodin **17** in 1936 (in a study partly funded by ICI),[250] griseofulvin **18** (in 1939)[251] and caldariomycin **19** (in 1940)[252] began a slow progression of reports that, by the time of Fowden's survey in 1968,[253] had amounted to only 30 or so natural organochlorine compounds. This enabled Doonan, in a review of the biochemistry of carbon–halogen bonds published in 1972,[254] to say 'The number of compounds containing covalently bound halogens which are produced by living organisms is very small'. On the other hand, Fowden, writing at the same time and more circumspect regarding the paucity of evidence, wondered 'just how restricted the distribution of this class of compounds would appear if a systematic survey of living organisms were made using more sophisticated methods for detecting halo-constituents?'.[253]



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CCl_4

20

$BrCH_2CH_2Cl$

21

CH_2ClI

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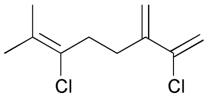

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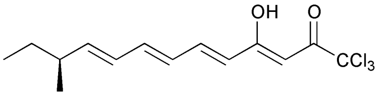

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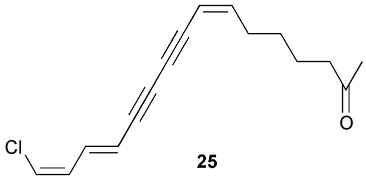

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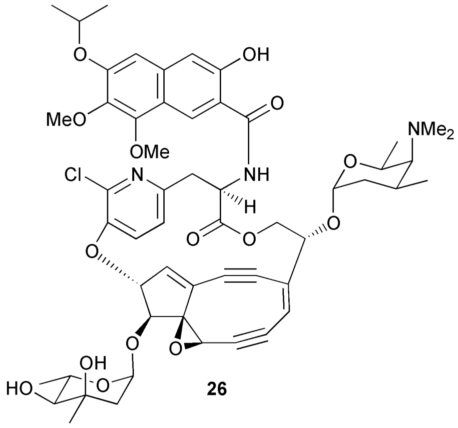

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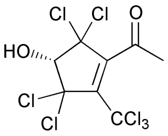

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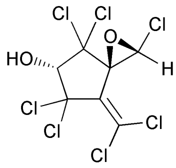

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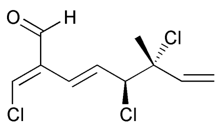
Fowden's scepticism proved well founded with evidence of the diversity of naturally occurring organohalogen compounds having become recognised only in the past 10 or so years, particularly since the First International Conference on Naturally Produced Organohalogens[255] in Delft in 1993. Gribble has been especially assiduous in tracking these developments in a series of authoritative and comprehensive reviews.[256–261] (See ref. 257 for a listing of earlier surveys). At the latest count (April 2000),[16] Gribble has documented 3357 organohalogens, 1978 of which contain chlorine. New reports now amount to several hundred per year. Wider awareness of, and appreciation of the significance of, the range of chemical types, the array of organisms which produce them, their distribution, abundance and role, is occurring more slowly. In 1993, the year of the Delft conference, it was possible to be told with apparent authority: 'Another category of materials which raise particular problems in the environment is that of synthetic substances; that is, substances which do not exist in any signficant quantity in nature, but only arise as a result of anthropogenic activities. Among this category, for instance, we find almost all the chlorinated organic compounds'.[262] As late as 1998, a review on drinking water disinfection by-products failed to draw attention to the natural contribution to the formation of such materials.[263]

In the section that follows, typical examples are given to illustrate the structural diversity of organochlorine compounds found in nature and the many chemical functionalities now known to be present in chlorine-containing compounds produced and transformed biotically and in other natural processes. This illustrative selection is not intended to be comprehensive. For this, the reader is referred to Gribble's compendious review of 1996[257] and later surveys. Later sections in this review deal with the sources, functions and transformations of organochlorine compounds. These will introduce additional examples of this class of materials.

3.2 Diversity

A large number of chlorine-containing C$_1$ - C$_2$ alkanes, such as **20**, **21** and **22**, are known, some with wide distribution and great abundance, arising from many terrestrial and marine sources, discussed further in Sections 4 and 5. Chlorinated alkenes **23**,[264] polyenes **24**[265] and alkynes (including polyacetylenes **25**[266] and enediynes **26**[267]) have also been described. Functionalised cycloaliphatics, such as caldariomycin **19**,[252] **27**[268] and **28**[268,269] isolated from the fungus, *Mollisia ventosa*, are also known and contain high proportions of covalently bound chlorine.

Marine and terrestrial organisms are responsible for the production of a wide range of terpene derivatives, many of which are halogen-containing. Chlorine-containing materials include monoterpenes, such as **29**,[270] alicyclic monoterpenes (*e.g.* **30**,[271,272] one of several isolated from the ubiquitous red alga, *Plocamium cartilageneum*) sesquiterpenes, such as jaeschkenol **31**,[273] from an Himalayan plant, diterpenes and higher terpenes.



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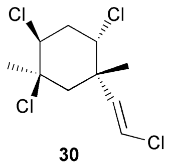

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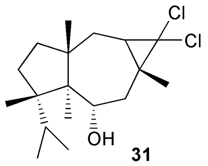

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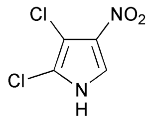

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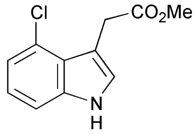

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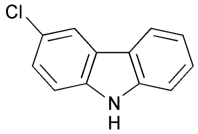

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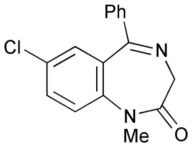

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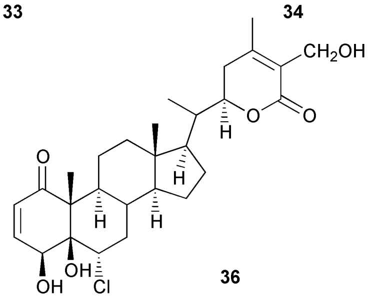

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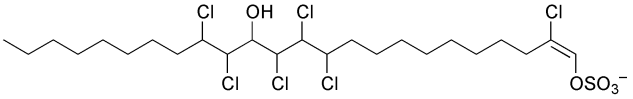
Heterocycles are exemplified by pyrroles, such as **32**,[274] a natural product (unusual in also having a nitro-group) with antibacterial properties, Tyrian purple **13**,[239,240] indoles with growth-promoting properties isolated from peas **33**,[275–279] carbazoles (*e.g.* **34** being a very rare example of a chloroorganic isolated from a mammal[280]) carbolines, furanones, benzofurans, and other aza- and oxa-heterocycles (including many glycopeptides, exemplified by the important antibiotic, vancomycin **1**). Surprisingly, chlorinated benzodiazepines (*e.g.* diazepam, 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one **35**) also have natural sources. Using monoclonal antibody techniques the existence in the brain of benzodiazepine-like compounds has been demonstrated.[281] Studies on brains stored in paraffin since 1940 (that is, prior to the introduction of synthetic benzodiazepines) and on a food product harvested in 1958 suggest that the presence of benzodiazepines, such as diazepam, does not arise from environmental contamination. Increased levels of benzodiazepines in germinating wheat and potato favour the view that these materials are of plant origin. That found in mammalian tissue probably arises from food intake. The amounts concerned are tiny, since about 10×10^3 t of potatoes would have to be consumed instantly for any pharmacological effects to be experienced.[281]

Chlorinated steroids (the first reported example being **36**[282]), the fatty compound malhamensilipin A (noteworthy for containing the 2-chlorovinylsulfate moiety **37**[283]), prostaglandins (*e.g.* **38**[284] from a brown alga), amino acids and peptides (such as the bis(trichloromethyl) derivative dysidenin **39**,[285] from a marine sponge), alkaloids (**40**,[286] a potent analgesic, from an Ecuadorean tree frog or **41**[287]), macrolides and quinones (3-chloroplumbagin, **42**[288]) have all been isolated and characterised from natural sources.



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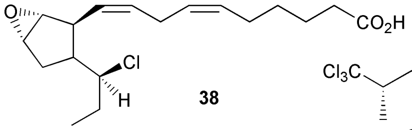

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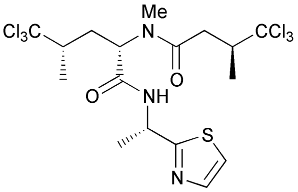

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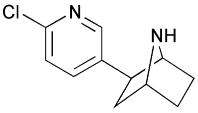

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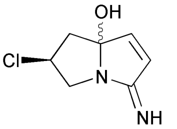

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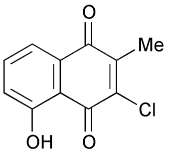

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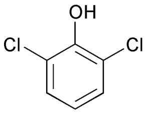

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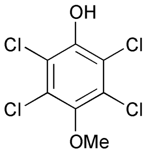

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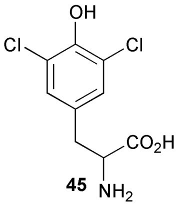

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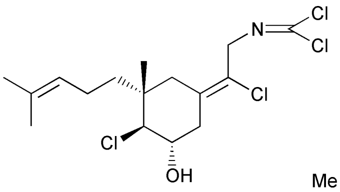
In addition, a range of phenols (*e.g.* **43**[289–291]) and the fungal metabolites **44**[292] and **8**[45] (representative of an extensively studied group of natural products discussed in more detail in Section 4.3), derivatives of tyrosine (such as **45**[293]) and more complex compounds containing carbonimidic dichloride **46**,[294] cyclopropane **47**,[295] cyclobutane **48**,[296] epoxy, lactone, *N*-oxide **49**,[297] isonitrile **50**,[298] and trichloromethyl **39**[285] and **51**[299,300] moieties have been isolated from bacteria, phytoplankton, fungi, algae and lichen, bacteria, terrestrial and marine plants, sponges, ascidians, bryozoans, worms, corals, insects, higher animals, frogs and humans, volcanoes, minerals and meteorites, sediments and soil.

Noteworthy among more recent developments is the isolation and partial characterisation[301] from the eggs of a range of sea birds of a series of halogenated bipyrroles, the most abundant of which is a 1,1′-dimethyl-tetrabromodichloro-2,2′-bipyrrole **52**. The highest concentrations (34–140 ng g^{-1} (wet weight)) are found in Pacific Ocean surface feeders, though significantly none is found in herring gulls from the relatively more polluted Great Lakes region of North America. Gribble *et al.*[302] have recently communicated the independent synthesis and characterisation of 5,5′-dichloro-1,1′-dimethyl-3,3′, 4,4′,-tetrabromo-2,2′-bipyrrole, the most abundant of the series isolated by Tittlemier *et al.*[301] The related hexabromo-2,2-bipyrrole is a known marine bacterial metabolite.[303] Seven organochlorine metabolites, **53**–**59**, isolated recently[304] from diseased bulbscales of the edible lily, *Lilium maximowiczii*, are believed to arise from enzymatic chlorination following infection by the fungal pathogen *Fusarium oxysporum f.* sp. *Lilii*.



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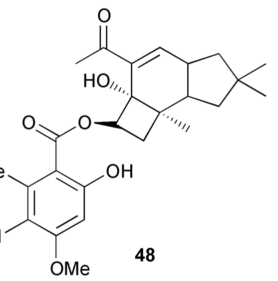

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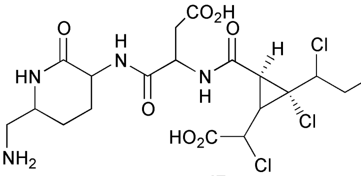

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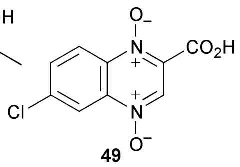

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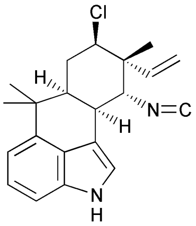

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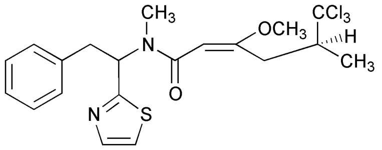

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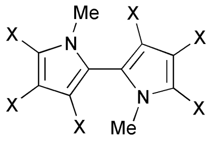
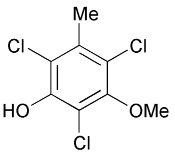


52 X = Br, Cl; $X_6 = Br_4Cl_2$



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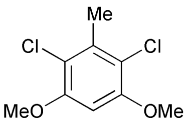

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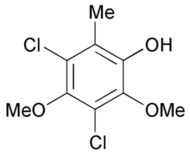

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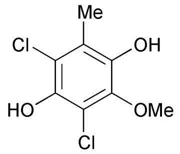

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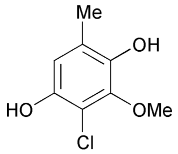

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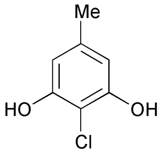

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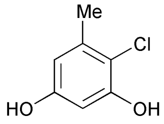

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3.3 Ubiquity

It is reasonable from the foregoing to conclude that organochlorine compounds may be present in all the earth's environmental compartments. (In fact, there is an early report,[305] independently confirmed,[306] that chlorine-containing compounds may be found, along with other predominantly aromatic material, in carbonaceous chondrites, that is, meteorites containing about 1% extractable organics. It is suggested[306] that these compounds arise from from equilibrium processes in the solar nebula, though their formation from reactions of chlorine atoms produced radiolytically by the interaction of chloride with cosmic rays cannot be ruled out. The possible extraterrestrial origin of organic compounds is a matter of current controversy.[307,308]) As inorganic chlorine is widely distributed throughout the earth's crust and the oceans,[51] it is also reasonable, *a priori*, to suggest that organochlorine compounds may also be produced naturally in any of these compartments. The fluxes of such naturally occurring chlorine-containing organics in and between these compartments and the associated sources, sinks and reservoirs would thus characterise a series of geochemical and biogeochemical cycles and sub-cycles. The nature and extent of these fluxes, sources, sinks and reservoirs will be determined by the processes which generate the chloroorganics, the physical properties of the compounds formed and the chemical and biochemical changes to which they may be subjected.

We discuss in this section some of the factors which govern the extent to which organochlorine compounds may be found and formed in the earth's major environmental compartments, *viz*. the atmosphere (Section 3.3.2), oceans and the polar ice caps (the 'cryosphere'), fresh-water bodies, such as rivers and lakes (Section 3.3.3), soil, sediment and groundwater (Section 3.3.4). Naturally formed chloroorganics differ widely in terms of their physical and chemical characteristics, being volatile, semi-volatile, involatile, hydrophilic and lipophilic, reactive or inert, depending on their chemical structure. As a consequence, a chloroorganic produced in one compartment may exchange into other compartments *via* gaseous, liquid or solid phase transfer and, thereby, become more widely distributed. Transfer into a different medium will lead to further opportunities for chemical and biochemical transformation and even ultimate mineralization to release inorganic chlorine.

These inter-reservoir or inter-compartment processes are particularly important for an appreciation of the global distribution of alkyl halides (Section 4.1), the origins and fluxes of trichloroacetic acid (Section 4.2), formation of fungal metabolites (Section 4.3), the origins and nature of soil-derived chlorinated organics (Section 4.4) and of 'dioxin' (Section 4.5).

To characterise fully a chlorine cycle, therefore, it will be necessary to (i) quantify the amounts of specific compounds, organic and inorganic, in the various compartments, (ii) identify their source strengths and fate, (iii) establish mass balances within defined compartments and sub-compartments of the different compounds of organic and inorganic chlorine, (iv) quantify the fluxes of compounds between and within compartments, (v) identify the physical processes by which transport and phase transfer are brought about, (vi) establish the precise mechanisms (and associated critical variables) by which chlorine-containing compounds are formed and the factors which influence the propensity for these processes to occur, (vii) measure the variation of these fluxes temporally (diurnally, seasonally), spatially (locally, regionally, globally) and climatically and (viii) characterise any interaction with other important elemental cycles and associated geochemical and geophysical phenomena, such as global atmospheric and oceanic circulation.

The collection of data on which such understanding will arise has hardly begun. The challenge is clearly linked with the complexity, inter-relatedness and dynamics of the processes which characterise the natural world. Some of these factors are introduced here. For further information the reader is referred to standard texts such as refs. 81–84 and 94.

3.3.1 Biotic *vs.* abiotic

Earlier sections have considered geochemical sources and fluxes of inorganic chloride. It is, of course, possible that chloride ion and HCl may generate organochlorine compounds naturally by chemical processes known to occur *in vitro*, provided suitable substrates are present under conditions in which a chlorinated product might form and accumulate. Volatile organochlorine compounds emitted from volcanoes may well have arisen from (possibly metal-catalyzed heterogeneous) chlorination and oxychlorination processes occurring at the elevated temperatures involved.[309] In addition, it has been proposed that chloromethane may arise from bromomethane or iodomethane by a simple nucleophilic displacement involving chloride ion[310–314] [eqn. (16)] (processes recently shown to be mediated enzymatically[222]).

$$\text{MeBr (aq)} + \text{Cl}^- \text{(aq)} = \text{MeCl (aq)} + \text{Br}^- \text{(aq)} \quad (16)$$

Abiotic halomethane formation has very recently been reported[315] to arise from the oxidation of guaiacol (2-methoxyphenol, a humic acid surrogate) by iron(III) (in the form of ferrihydrite ($5Fe_2O_3{\cdot}9H_2O$)) in the presence of halide ion.

With brominated compounds such as bromoform being formed in large quantities ($0.1–1.0 \times 10^6$ t per year) particularly in the polar regions, it is likely that $CHCl_3$ and the mixed haloforms, $CHClBr_2$, $CHCl_2Br$, may also arise, at least in part, by halide-exchange reactions.[316] By analogy, this allows the speculation that reaction of chloride ion with ethylene dibromide, detected in significant quantities in ice pools in the Arctic,[317] may lead to 1-bromo-2-dichloroethane and ethylene dichloride. The latter has hitherto been thought to be entirely man-made, being produced (though not emitted) in huge quantities industrially for conversion to vinyl chloride and thence to PVC. This example serves to underline the importance of the need fully to characterise and understand the chlorine cycle and its inter-related natural and anthropogenic components.

Organochlorine compounds also arise *via* biochemical chlorination (discussed in detail in Section 5). In fact, reaction 16 is now known to be enzymatically catalyzed by a soil organism, though much more extensively studied are the enzymatic reactions involving peroxide-induced oxidation of chloride ion which give hypochlorous acid. There is also evidence that hypochlorous acid may be formed from peroxidases, hydrogen peroxide and chloride ion in soil. Such processes may lead to a range of products of electrophilic chlorination derived from soil organic matter such as humic and fulvic acids. The extent to which these reactions should be viewed strictly as biotic or abiotic chlorinations is a moot point and will be governed by the degree to which free hypochlorous acid is released to the ambient environment. We have also seen that so-called 'reactive' chlorine (possibly HOCl or a reservoir of electrophilic chlorine, such as $ClNO_2$, $ClONO_2$) may be formed on or in sea-salt aerosol by oxidation with O_3, NO_3 or NO_2. While there is, so far, no evidence that such reactive chlorine is the source of organochlorine compounds this cannot be entirely ruled out.

Whatever their function, and this is discussed in Section 3.4, it is undoubtedly the case that many chlorine-containing organic natural products are to be found in the aqueous and terrestrial environment and in the atmosphere, being formed biotically (from bacteria, phytoplankton, fungi, algae and lichen, terrestrial and marine plants, sponges, ascidians, bryozoans, worms, corals, insects, frogs, higher animals, including humans) and from natural geochemical and atmospheric processes. Gribble has very recently surveyed[259] organochlorine compounds from the point of view of their origins. The presence of organochlorine compounds in coal deposits testifies to the ancient capacity of the earth to produce compounds containing carbon–chlorine bonds. Reports of their isolation from carbonaceous meteorites point to possible extra-terrestrial sources.[305,306]

3.3.2 Atmospheric

The atmosphere, including the troposphere and stratosphere, will be the most important reservoir for volatile compounds, including halogen- and chlorine-containing organics. Emissions to the atmosphere will arise from the oceans, seas, lakes and rivers, from volcanic activity (a recent report[318] suggests that, of > 300 organic compounds emitted from four volcanoes, 100 were chlorine-containing), from land-based biota (arising directly from natural biological processes and from the combustion of biomass), from soils and, of course, from human activity in all its forms. Emissions may occur directly or the chloroorganic may be conveyed into the atmosphere by aerosols and particulates, arising from wind and wave activity at the surface of the seas and oceans, from dust particles originating from soil erosion, volcanic activity or from soot arising from combustion processes. Losses from the atmosphere may involve transfer to (and *via*) such particulates (and precipitation) which themselves may be deposited on the seas, polar ice-caps and land masses. An organochlorine, emitted locally from a point source, will be dispersed and diluted by the expected physical processes driven by concentration and temperature gradients and by meteorological processes driving the movement of air masses, locally and globally. Atmospheric transport *via* particulates (*e.g.* of the dioxins or polychlorinated biphenyls, PCBs) and in precipitation (*e.g.* of the haloacetic acids, such as trichloroacetic acid) are important processes for the movement of semivolatile, involatile and hydrophilic compounds, even though there is a negligible atmospheric burden of these materials. Some losses occur *via* the stratosphere to space. Global circulation, meteorological and climatic factors, and inter-hemispheric exchange will lead to transport and mixing. The burdens of a particular material detected at a particular point in space and time will be governed by an integration of these various factors along with its atmospheric lifetime, linked to the susceptibility of the material to atmospheric degradation, particularly by photochemical or oxidative decomposition. (The role of hydroxyl radicals and the possible involvement of chlorine atoms in this latter process has been discussed in Section 2.5.)

As noted earlier, the Reactive Chlorine Emission Inventory (RCEI) study has provided the most authoritative assessment to date[55–62] of the distribution of the sources (natural and anthropogenic), reservoirs and fluxes of the most important atmospheric chloroorganics (chloromethane, dichloromethane, chloroform, trichloroethylene, tetrachloroethylene). However, indicative of the uncertainties in the available data (including such fundamental parameters as Henry's Law constants (see, for example, ref. 319)) and the tentative and provisional nature of conclusions based on them, the RCEI study has revealed that the sources of chloromethane, the best studied of all the organohalogens, may need to be split more evenly between marine and terrestrial sources. In addition, insufficient source strengths have been identified to account for the $(3–5) \times 10^6$ t annual production necessary to maintain its global mean tropospheric concentration. The hunt for additional sources of $(1–2) \times 10^6$ t per year of chloromethane is now on. Recent studies have focused on salt marshes, wetlands and ruminants as possible sources. Coastal salt marshes, in which chloromethane-producing halophytes, such as *Mesembryanthemum crystallium* and *Batis maritima*,[320,321] grow in great abundance, give rise to an estimated 170×10^3 t of chloromethane of natural origin.[322] Recent atmospheric halomethane measurements[323, 324] confirm the potential importance of coastal sources. Estimates based upon studies of wetland sites in the northeastern USA suggest that the global annual flux of MeCl from this source may be only *ca.* 50×10^3 t.[325] CH_3Cl emission from cattle is an insignificant source amounting to only *ca.* 1×10^{-3} g/cow/day (compared with *ca.* 150 g methane/cow/day) (amounting to a total source strength from cattle worldwide of *ca.* 500 t per year).[326] Natural formation of volatile halogenated methanes has been reviewed by Wever[327,328] and Harper.[329–331] Of relevance are two recent reports[332,333] which conclude that higher plants may be both sources and sinks for bromomethane in the atmosphere.

Chloromethane is approximately uniformly distributed in the atmosphere, consistent with predominantly natural sources, at a concentration of *ca.* 600 pptv. There are few studies of its seasonal variation,[74] but such variation appears to be linked with the cycle of $OH^{\bullet}$, the oxidant which initiates MeCl removal from the atmosphere. About 85% of the MeCl emissions arise in the tropical and sub-tropical latitudes, between 30° S and 30° N. While marine sources, such as algae and phytoplankton, have previously been considered most important (see Section 4.1), a reassessment of the inputs from terrestrial sources, such as biomass burning,[62,334–338] and from wood-rotting fungi,[339] is timely.

Crutzen *et al.* were the first to detect chloromethane as a product of biomass burning.[334] Global emissions, based on a small savanna region in Western Africa, were estimated to be *ca*. 0.5 × 10^6 t per year.[335] Biomass burning is also an important source of dichloromethane and a possible minor source of C_2Cl_4, C_2HCl_3, $CHCl_3$ and CCl_4. The amounts produced are dependent on the types of biomass burned, its chloride content, combustion efficiency and the rate of heat release.[336] It has been estimated that *ca.* 70% of chloromethane emitted during biomass burning occurs at the smouldering stage.[340] The best estimates of global emissions are 0.64 × 10^6 t Cl per year for MeCl and 49 × 10^3 t Cl per year for CH_2Cl_2.[62]

An early report of the formation of chloromethane by potato tubers[341] (a minor source) has recently been confirmed,[342] with a biogenic origin established[342] rather than the initially proposed accumulation from the atmosphere.[341]

In addition to the C_1 species, chloromethane, dichloromethane, chloroform, carbon tetrachloride, partially brominated and iodinated analogues, and even chlorofluorinated materials (such as $CFCl_3$, CF_2Cl_2,[318,343–345] in volcanic gases emitted to the atmosphere at 10^3 to 10^4 times background concentrations, though contributing only minimally to the global burden of these compounds), higher chloroalkanes, including derivatives of propane, butane and pentane, have been reported, largely from marine sources such as algae, studied *in situ* or in the laboratory. Unfortunately, accurate source data for chlorine-containing alkanes, other than the simple C_1 and C_2 chloroorganics, are few and flux estimates even less reliable.

Chloroform, with an average atmospheric concentration at the earth's surface of 18.5 pptv and a global emission rate of (0.35–0.60) × 10^6 t per year,[75] has both marine and terrestrial sources, from algae, fungi,[346] trees and fruit. It is also transformed from brominated precursors by halide exchange and arises from soil processes involving humic materials, chloroperoxidase, exocellular hydrogen peroxide and chloride ion (see Section 4.3). Australian termites are known to produce chloroform at 1000 times higher concentrations in their mounds than in ambient air and give rise to a signficant flux to the atmosphere.[347] Soil fungi also produce chloroform *de novo*[346] and release it to soil air. From studies in Danish forests,[348] chloroform concentrations in soil air were, respectively, 6.7-, 4.3- and 4.6-fold higher than ambient for spruce forest, beech forest and grassland. Release-rate studies in a spruce forest point to a biogenic origin.

Atmospheric and oceanic analyses (including several reports of oversaturation of trichloroethylene and perchloroethylene in the remote oceans) and inventories of industrial production and use point to significant larger global fluxes of the industrially important solvents (used predominantly in dispersive uses) trichloroethylene, perchloroethylene and dichloromethane than can be accounted for from anthropogenic sources. In fact, the recent Reactive Chlorine Emissions Inventory study has concluded[56] that *ca.* 25% of CH_2Cl_2, 10% C_2HCl_3 and 5% of C_2Cl_4 detected in the atmosphere are emitted from the oceans. Recent reports that algae produce trichloroethylene and perchloroethylene[349–351] have not been confirmed, however,[352,353] though evidence for natural sources of both trichloroethylene[354] and perchloroethylene[355] continues to be reported.

Recent evidence for the role of chlorine atoms as atmospheric oxidants will focus attention on the possible formation of compounds with carbon–chlorine bonds in the atmosphere from reaction with chlorine atoms and their abundance, flux and function. The primary product of the reaction of chlorine atoms with hydrocarbons present in the atmosphere is expected to be HCl, formed by hydrogen-atom abstraction. However, addition of chlorine atoms to unsaturated atmospheric components is also possible, though subsequent reactions may simply lead to complete oxidative breakdown. Very recently, though, Finlayson-Pitts and co-workers[217] have suggested that isoprene, an important naturally occurring hydrocarbon in addition to generating non-chlorinated oxidation products during atmospheric breakdown mediated by chlorine, produces the chlorine-containing product 1-chloro-3-methyl-3-buten-2-one **10**. Such compounds may, therefore, act as markers ('sentinel' compounds) for inorganic reactive chlorine in the atmosphere.

In addition to being an important vehicle for removing inorganic chloride from the atmosphere, precipitation in all its forms can do the same for hydrophilic chloroorganics, such as the chloroacetic acids. Global atmospheric circulation ensures that such precipitation in remote regions, such as the Arctic and Antarctic, may contain such material, depending on their distribution (and that of their precursors) and atmospheric lifetime. The environmental chemistry of the chloroacetic acids is dealt with more fully in Section 4.2.

Precipitation in the form of partially consolidated snow ('firn') may trap ambient air. In the polar regions where such material collects continuously, analysis of the trapped air for trace haloorganics has allowed depth (and hence age) profiles for these materials to be obtained (below about 30 m, transport of constituent gases is believed to occur mainly by molecular diffusion). Using air samples from firn collected at three sites, two in the southern hemisphere, Butler *et al*.[356] have established preliminary histories for the concentrations of CFCs in firn air consistent with their recent anthropogenic origin. The concentration of chloromethane over most of the 20th century appears to have been roughly constant.

3.3.3 Hydrosphere

3.3.3.1 The seas and oceans

The hydrological cycle links the oceans, the earth's crust, land surface, including lakes, terrestrial ice fields and groundwater, and the atmosphere. The water fluxes between these reservoirs are prodigious. Their importance in the cycle of inorganic chlorine has already been described.

To an extent limited by the availability of appropriate nutrients and energy sources, the oceans' biota (see, for example, Fig. 2 of ref. 357) is dependent on the production of organic matter by the primary producer, phytoplankton. Photosynthesis occurs in a relatively shallow surface layer ($<$ 200 m). Primary production can also occur in the isolated ecosytems located near hydrothermal vents. An important component in the seas' life-cycles is the production and consumption of particulate organic matter (arising from the excretion from and death of marine organisms) either in suspension or following deposition in marine sediments.

The organic chemistry of marine metabolites is, surprisingly, itself only a relatively recent area of major study.[357] Most of the marine organic matter comprises compounds of carbon, hydrogen, oxygen, nitrogen and sulfur. Some of these will be volatile or capable of dissolving or being solubilised in seawater. These can be transported and lost from the oceans to the atmosphere, accumulated by other organisms, transformed chemically or biochemically to other compounds or completely decomposed to inorganic species, such as water, bicarbonate, nitrate and sulfate. The fate of these marine organic compounds will depend on their stability and reactivity and the location of their production. It is possible that they may be adsorbed onto particulates and deposited in sediments and ultimately be processed by diagenesis into crustal rocks. The seas are the source of a wide range of exquisitely complex organic compounds, a proportion of which are also halogen- and, more particularly, chlorine-containing. The structural types and functionalities represented among the non-halogenated metabolites are also typical of those seen for halogen-containing metabolites, suggesting that the latter do not represent a unique class of marine natural products. Such compounds are produced by various marine organisms, including seaweed, microalgae and phytoplankton, sponges, sea hares, sea slugs, coral and fish. Bearing in mind the enormous oceanic production of biomass in the presence of chloride ion at *ca*. 0.1 M NaCl, it would be surprising if this were not the case. Future research will undoubtedly add to the number and diversity of both chlorine-containing organics and chloro-organic producing organisms.

Marine sources of the halomethanes are discussed in more detail in Section 4.1. Volatile organochlorines produced by marine organisms will partition into the aqueous phase and be transported, vertically and horizontally, along oceanic currents and to the sea-surface where they will equilibrate with the ambient atmosphere. It is possible that some of the volatile organochlorine compounds found in the sea may have originated from atmospheric (and from terrestrial) sources and have partitioned into the sea in the reverse of this process. Local high marine production of a volatile organochlorine may lead to the phenomenon of oversaturation (governed by factors such as sea temperature and the compound's concentration in adjacent air masses and their temperatures). Observation of such phenomena may provide support for a natural marine source of an organohalogen, but this is not invariably the case. For instance, a volatile organohalogen in the atmosphere may equilibrate with a sea mass with which it is in contact at a low temperature. The sea mass may then be transported to a region of higher temperature. Slow sea-to-air mass transfer may lead to oversaturation. The tendency therefore for the sea to be either a source or sink for volatile organohalogen compounds (such as the haloalkanes and haloalkenes) is evident and arguments for a natural source based on oversaturation should be treated cautiously in the absence of additional evidence. This is discussed further in Section 4.1.

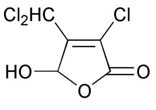
Involatile organochlorine compounds produced by marine organisms may be deposited in marine sediment on excretion or on the death of the organism. Some may be solubilised by marine surface-active agents and collect in the lipophilic microlayer that exists on the surface of natural waters, including the oceans.[176,358] It is possible that some of the organic material which collects at the ocean surface may be entrained in sea-salt aerosol and be subject to further physical transport and possible chemical change (including chlorination, though evidence on this latter point has not so far been described).

Some organochlorine compounds, natural or anthropogenic, will also find their way into the seas as components of river water. Much of this will be so-called adsorbable organic halogens (AOX) derived from humic material arising from the breakdown of vegetation and other biotic debri. Some mass balance studies of the transport to the sea from the drainage of river systems have been undertaken which confirm the need to recognise natural sources in addition to anthropogenic.[359] The deep sea has been suggested[360,361] as the ultimate global sink for persistent organic pollutants.

3.3.3.2 Rivers and lakes

Fresh-water natural sources of organochlorine compounds are also known, arising from aquatic organisms or by processes associated with the transformation and degradation of soil organics, particularly fulvic and humic acids. Establishing that, in part at least, these chlorine-containing products are truly of natural origin has posed a number of experimental and analytical challenges, not least associated with their polydispersity and complex nature. In fact, the greater part of such organochlorines is extremely difficult to characterise and is known collectively as AOCl (adsorbable organic chlorine). Much of that finding its way into rivers or streams is likely to have originated from waters leaching or draining from the soils (see Sections 3.3.4 and 4.4). Very little is known of their precise chemical structure, though some clues arise from an awareness of common structural elements found in humic substances, from studies of model systems and from the nature of chlorinated aromatic and other compounds isolated from soil environments.

Additional complexities have arisen because of the chemical similarity (and in some cases identity) between anthropogenic pollutants (or their degradation products) and materials generated naturally, as well as the similarity of the chemical processes responsible for natural chlorination of humic materials and those involved in water disinfection using chlorine. It is an intriguing possibility that mutagenic compounds detected in water treated with chlorine, such as **60**, and thought to have arisen from humic materials as a consequence of such treatment, may also arise through similar processes involving natural chlorination.



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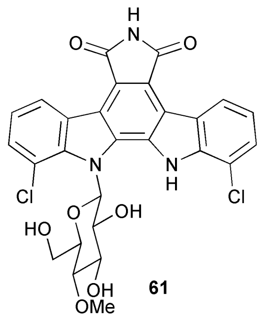

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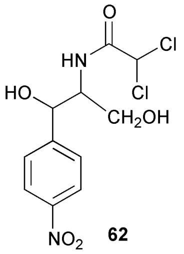

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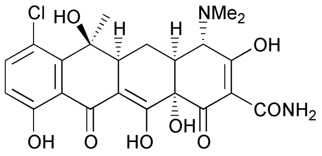

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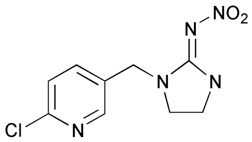

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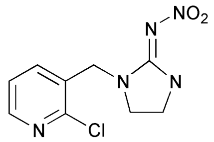

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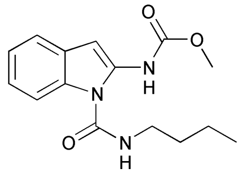

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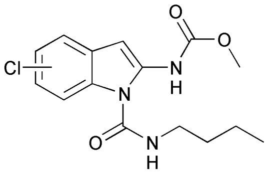

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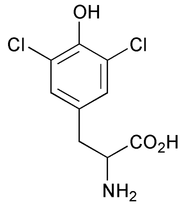

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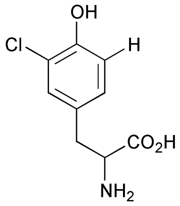

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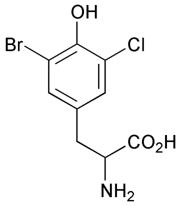

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Particular environmental concerns have arisen from the release into the aquatic environment of chlorinated materials in the form of pulp mill effluent associated with chlorine bleaching processes in paper making. Such effluent comprises a complex mixture of several hundred chlorinated organics. Fresh water mussels, *Anodonta anatina*, from an unpolluted lake in Finland, incubated for 12 months in a lake which received pulp- and paper-mill effluent, led to an extractable organic halogen (EOX) content of the mussels of 2045 μg g^{-1} of lipids, pointing to significant bioaccumulation of organochlorines.[362] Of interest, however, was the observation that the mussels prior to exposure to the polluted lake contained 690 μg EOX g^{-1} of lipids. While atmospheric deposition might account for some of the detected organochlorines in mussels from the unpolluted lake, it was concluded that an additional natural source was necessary. Evidence that the chlorinated fatty acids, particularly dichloromyrisitic acid, present in mussels and fish, may be of partly natural origin is discussed by Mu *et al.*[363,364] Similar material, quite probably the 9,10-isomer, $CH_3(CH_2)_3CHClCHCl(CH_2)_7CO_2H$, has also been isolated from the digestive gland of lobster.[365] (The care needed in approaching the discussion of the possible natural or anthropogenic origin of a chlorinated organic in such systems is underlined by the observations of Hamilton *et al.* who have shown that bacteria grown on chloroalkanes may incorporate chlorine into long-chain fatty acids in cellular lipids rather than effect complete mineralization.[366,367]) That the AOX present in river systems may, in part at least, be of natural origin is supported by observations on the river Rhine discussed in more detail in Section 4.4.[368–370]

3.3.4 Pedosphere

3.3.4.1 Soils

The soil comprises an intimate, complex and dynamic mixture of minerals and the organic debris ('humus') from dead plants, animals and microorganisms, undergoing chemical and biochemical aerobic and anerobic change on various timescales, with some of the products of such change being released into soil air (which will slowly equilibrate with the ambient atmosphere) or dissolved, solubilised or suspended into water deposited as precipitation, and which leaches through the various soil layer into groundwater. The chemical transformations of humic materials have recently been reviewed.[371]

The health and productivity of soil is vital for its continuing contribution to photosynthesis as well as its use in agriculture. In the latter context, a current controversy surrounds the use of bromomethane as a soil fumigant. Accurate estimates of the emissions of bromomethane from soil are necessary for a proper assessment of the contribution of such an agricultural use to ozone depletion by bromomethane. Uptake of bromomethane by soils has thus been subjected to various studies. (See for instance refs. 372, 373 and a recent relevant report.[222])

Organochlorine production in soil and sediment has been less extensively investigated. Local, regional and episodic studies however have permitted tentative estimates of the quantities of organochlorine compounds present to be made. For example, Öberg[85] has concluded that the chlorine content of organic material in soil is similar to that of phosphorus, thus highlighting a significant though largely overlooked constituent of soil.

Soil organisms are important potential sources of organochlorine compounds. For instance, an actinomycete, *Saccharothrix aerocolonigenes*, isolated from a soil sample from Panama, in culture biosynthesis,[374] rebeccamycin **61**, reported to inhibit the growth of human lung adenocarcinoma cells.[375] The role of fungi, known to produce both volatile and involatile organochlorines in considerable quantities, is dealt with in more detail in Sections 3.4 and 4.3.

Studies reviewed by Öberg[85] suggest that the organic matter to be found in temperate evergreen forest soils contains 0.05% of organically bound chlorine. The degree of chlorination increases with soil depth (possibly associated with leaching), reaching 2–10 mg organically bound chlorine per g organic carbon. Estimates of the reservoir of organically bound chlorine in the top 60 cm of such soil range up to 0.6 t ha^{-1}. The factors which control productivity and distribution of these materials have been little studied.

In addition to the introduction of pollutants, organochlorines in soil may arise from deposition from the atmosphere, from vegetation or from processes of soil chemistry and biochemistry[371] (such as may arise from the presence of chloroperoxidase-like enzymatic activity in soil[376]). It is believed[85] that processes of chlorination are particularly efficient since the net rate of organochlorine formation is independent of chloride ion concentration in the soil (which varies from a few to hundreds of ppm). Natural organochlorine production is proposed to account for the four-fold greater average total organic chlorine content of water draining from 32 different forest and bogs in Finland compared with the rain water deposited on the forests and bogs.[377]

Immobilization (and remobilization) of organochlorines in soil humus has also been reported, with such studies, having initially been devoted primarily to discovering the fate of chloroorganic pollutants, now demonstrating that naturally occurring analogues may also be involved.[378–384] It is likely that similar processes will also immobilize and remobilize chlorine-containing materials that arise *de novo* in the soil by natural processes. In laboratory studies, complete reductive dechlorination of trichloroethylene (giving ethane and ethylene as the major products) was reported[385] to occur involving titanium citrate and nickel complexes of humic acid, giving rise to the speculation[385] that humic acid–metal complexes may mediate related reductions in the environment. Other recent studies have suggested that humic substances may effect dioxin dechlorination.[386]

3.3.4.2 Sediments

Sediments arise from the deposition of fine particulate matter (and entrained water) from lakes, rivers, estuaries and the seas. Sediment will thus comprise both mineral, organic and living material, some dissolved in pore water, some adsorbed on the surface of particles. Chemical and biochemical transformation will also occur on a range of timescales, though bearing in mind the location of sediment with limited access to atmospheric oxygen, these are likely to be predominantly anaerobic reductive processes. Some physical transport may take place within these sediments associated with the movement of organisms ('bioturbation'). However, at depth in thick sediment bioturbation may be quite limited, enabling depth-profiling and aging to occur, so that the history of the sediment and its composition may be traced ('paleolimnology' or 'chronostratigraphy'). This has enabled the build-up and transformation of pollutants to be studied, and the presence of materials such as dioxins in the sediments to be traced back to before the advent of large scale purposeful production, use and emission of organic compounds containing chlorine.

3.3.4.3 Groundwater

Accumulation of groundwater in aquifers provides important sources of drinking water.The presence of any potentially toxic material in such water bodies will be of concern. The poor storage and unacceptable disposal practices of hydrocarbon and chlorine-containing organics has resulted in the contamination of some groundwaters used for the supply of drinking water.

However, groundwater collects having trickled though the soil ('infiltration'), after having been deposited on the soil in the form of precipitation. Such precipitation may contain organics (some of which may be chlorinated) washed out from the atmosphere (or contain particulates as condensation nuclei on which semivolatile or involatile organics (some chlorine-containing) have been deposited). Further organic material may be picked up from vegetation with which the precipitation comes in contact before entering the soil ('throughfall').

The residence time for groundwater may be very long, so the detection of chlorinated organics (such as AOX) in aquifers containing water as old as the end of the last ice age would provide further evidence that some organochlorine compounds have ancient origins. However, determination of the age of dissolved organic material by ^{14}C isotope measurements is fraught with difficulties and uncertainties remain in their interpretation. Chlorinated organics in groundwater may be subjected to both aerobic and anaerobic degradation, the former being associated with groundwater closer to the surface. Release of chloride ion may lead to materials with a lower degree of chlorination. Furthermore, the processes of chemical and biochemical breakdown may generate products of low enough molecular weight or with appropriate functionality to permit the release of halogen-containing compounds from sediment into groundwater.

Much more data are required (and of greater precision) before it is possible to quantify the sources, fluxes and sinks of organochlorine compounds for an overall chlorine cycle However, it is pertinent to point out the very great difficulty in unequivocally distinguishing between those materials which arise directly from the release of man-made organochlorine compounds (or which are produced adventitiously from industrial processes), those formed by human non-industrial activities, those generated naturally and those transformed in the environment. This important aspect is dealt with in Section 7.

It is however now beyond reasonable doubt that the presence of organochlorine compounds in the environment predates the advent of the modern chlor-alkali industry and even the period which saw the evolutionary development of early man. Evidence exists (some of which is discussed in more detail in Section 4.4) of the presence of organochlorine compounds in ancient coal deposits of pre-historic origins, in sediments and groundwater thousands years old and even in meteorites.

3.4 Function

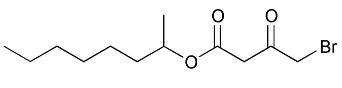
Having established that natural compounds of chlorine are abundant, widespread, chemically diverse, and produced (and released) by many different organisms, it is reasonable to address how these compounds arise (discussed in Section 5.1), whether these materials have any identifiable function and, if so, what these might be. The few instances where these questions have been addressed are described below. This should become a very active and fruitful area of future research.

Much of the early interest in organochlorine metabolites centred on the antibiotic properties of fermentation products, such as chloramphenicol **62**, griseofulvin **18**, aureomycin **63** and vancomycin **1**.[387] However, later work on the toxicology and pharmacological properties of some reactive polychlorinated organic pollutants led to the generalisation[22] that the presence of chlorine must automatically render a compound more toxic than its non- or less-chlorinated analogue. In a recent survey, Naumann[388] using hitherto unpublished data, finds this generalisation to be erroneous, showing, not surprisingly, that organically bound chlorine may behave like any other chemical substituent to affect, either beneficially or deleteriously, some required characteristic in fulfilling a particular biological or pharmacological function, often by position rather than by mere presence. This may be illustrated with three of the many examples assembled by Naumann: replacement of the 4-chloro by H in griseofulvin **18**, or moving it to the 2-position, renders the material inactive; the highly active insecticide imidachloprid **64** is rendered barely active by a shift of the 2-chloro to the 6 position, as in **65**. The well known (non-chlorinated) fungicide benomyl **66** is rendered much less active by the incorporation of a chlorine into the benzene ring **67**.

Chlorine affects the physiological or biological properties of a molecule by altering its physical or chemical properties. It is the differences in combinations of effects, governing the solubility, polarity, partition coefficient, enzyme active-site binding constant and reactivity, that control the differing biological properties of a pair of molecules, differentiated only by the presence, absence or site of substitution of a chlorine atom. The chlorine atom need not be reactive to have a biological effect. It may change the acidity or basicity (or electrophilicity or nucleophilicity) of a nearby group through inductive or conjugative transmission of its electronic influence. Because of its relatively large van der Waals radius, it may affect non-bonding interactions at active sites or even dictate conformational preferences necessary for biological activity. (In the case of the antibiotic vancomycin **1**, chlorine is found to be crucial in enforcing the required conformation to achieve receptor binding.[389]) Chlorine's lipophilicity and effect on dipole moment may also affect solubility and partitioning. It may engage in hydrogen-bonding. A chlorine substituent may render a molecule more reactive, hydrolytically, reductively or oxidatively. It will be a combination of all these factors that governs at the molecular level the physiological role of organochlorine compounds produced by organisms and their effect on other organisms with which they come in contact. The overall conclusion is that chlorine is not an intrinsic toxophore.[388]

It seems likely that, in some cases at least, living organisms produce organochlorine compounds to fulfil specific purposes, though at present these functions are poorly understood. For example, formation of volatile organochlorine compounds, such as chloromethane, may effect the removal of chloride ion. Saini *et al*.[390] have proposed that higher plants which find halide ion (and hydrogen sulfide ion) phytotoxic may eliminate them in this way. On the other hand, bearing in mind that the generation of oxidants, such as hypochlorous acid, is used for biological defence, such as phagocytosis, it is also possible (as most organisms appear to accumulate halide ions in excess of the minimum needed for normal growth[253]) that some chlorinated organics arising from hypochlorous acid are adventitious by-products devoid of utility. The recent report[15] that tyrosine residues in human low density lipoprotein may be chlorinated *in vivo* by the body's defence processes may provide such an example, though more work needs to be done to establish this point. Bearing in mind the association of the chlorinated protein with atherosclerotic lesions, a possibly fruitful line of enquiry may arise from work on the role that chlorine-containing tyrosines, such as **68**, **69** and **70**, found in proteins, isolated from the cuticle of locusts[293] and from molluscs,[391] play in the enhanced adhesion between protein fibres and sheets.[392] In the human body, halogenated products such as thyroxine **11** have an established physiological role and the brominated product, 1-methylheptyl-γ-bromoacetoacetate **71**,[393,394] probably so, but this requires further study (see Section 5.3).

On the other hand, organohalogen compounds in general and organochlorine compounds in particular are purposefully produced for defensive purposes (and as anti-feedants), particularly by a range of marine organisms. For example, *Haminoea cymbalum* (the Guam 'bubble shell') uses kumepaloxane **72** as a feeding deterrent against carnivorous fish.[395] **72** is exuded in the mucus when the organism is disturbed. It is not known whether **72** is acquired by the organism in its diet or whether it is biosynthesized. However, it is not found in the green alga *Canterpa racemosa* on which the bubble shell grazes. The sea-slug, *Diaulula sandiegensis*, is also known to secrete a number of chloroacetylenes (*e.g.* **25**[266]) as defensive agents. The organochlorine metabolites **53–59**, isolated[304] from diseased bulb scales of the edible lily, *Lilium maximowiczii*, function as antimicrobial compounds ('phytoalexins') in a process of dynamic resistance. The fact that these naturally formed pesticides are unstable points to the possibility of designing chlorine-containing pesticides with lower environmental persistence. Epibatidine, a toxin isolated from the skin of the Ecuadorian tree frog, *Epibobatides tricolor*,[286] having the structure **40**, was subsequently found to have analgesic activity significantly greater than that of morphine. The activity arises from a completely different mechanism of action. Because it is possible that a class of pain-killers devoid of the dependency problems of morphine may arise, several pharmaceutical companies have taken an interest in epibatidine to establish wholly synthetic routes.[396,397] However, epibatidine itself was



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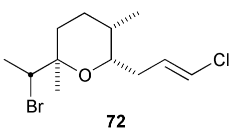

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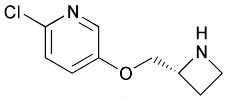

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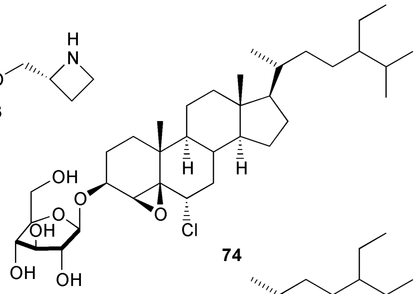

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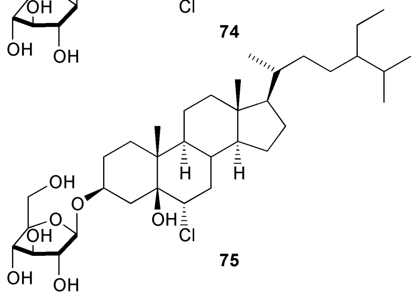

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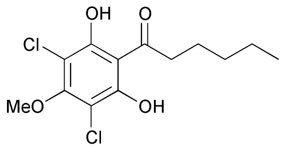

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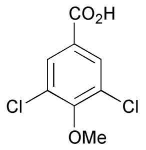

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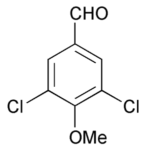

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found to be unacceptably toxic. Synthetic analogues such as (*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine **73** have been subsequently identified with improved therapeutic ratios with, significantly, chlorine still needed for activity.[398]

In contrast, the chlorinated compounds 2,6-dichlorophenol **43** and blattellastanosides A **74** and B **75** behave as attractants rather than repellants, that is, as insect pheromones. The phenol acts as a sex pheromone for several species of tick.[289,290] Studies of the incorporation of ^{36}Cl from ^{36}Cl-enriched NaCl into 2,6-dichlorophenol establishes a *de novo* synthesis by the tick.[291] The German cockroach, *Blattella germanica*, uses **74** and **75** as aggregation pheromones to mark its harbouring sites.[399] The use of ^{36}Cl-labelling also reveals *de novo* synthesis[400] of 1-(3,5-dichloro-2,6-dihydroxy-4-methoxyphenyl)hexan-1-one **76**, produced by the slime mould, *Dictyostelium discoideum*, to trigger morphogen differentiation, that is, the transformation of undifferentiated cells into fruiting bodies.[401] 4-Chloroindole-3-acetic acid **33** (first isolated from peas in 1968[276,277]) and its methyl ester, are among a number of chlorinated compounds isolated from higher plants.[278] It is known from ^{36}Cl labelling experiments[278] that many such plants incorporate chloride ion into organic compounds similar to the chloroindole derivatives. Compound **33** and its methyl ester have been shown to be present at between 0.01 to 10 mg kg^{-1} (fresh weight) in a range of leguminous plants such as green pea, sweet pea, lentil, vetch. They are believed to be natural plant growth hormones involved in seed development.[279]

The extensive study of the formation of chlorinated secondary metabolites from fungi (see Sections 4.3 and 5.1) has included investigation of their possible function. Harper has demonstrated[402–410] that chloromethane acts as a methylating agent or methyl donor in the biosynthesis of anisoles and methyl esters by a range of fungi (some, in fact, not chloromethane emitting) involved in the degradation of lignin.[411] The related chlorine-containing anisyl metabolites *e.g.* **8**, **77**, **78** studied by de Jong *et al.*[412,413] have a physiological role in lignin degradation, serving as substrates for aryl alcohol oxidases involved in extracellular hydrogen peroxide production. This is further described in Section 4.3.

Bearing in mind its ubiquity, massive global natural production and atmospheric lifetime, tropospheric chloromethane currently contributes significantly to the chlorine loading in the stratosphere.[134,135] As there are likely to have been marine and terrestrial natural sources of chloromethane for as long as algae, fungi and other organisms have existed, chloromethane will have been involved in processes of catalyzed stratospheric ozone decomposition over a similar period. Lovelock has, thus, proposed that chloromethane acts as a natural regulator of stratospheric ozone.[52,53] It is not known whether or not the absolute contribution to stratospheric chlorine loading from chloromethane has remained constant over time. However, bearing in mind that one source, rotting wood, is likely to have declined significantly over human history because of deforestation, it is possible that the current contribution from this source is also lower than before significant forest clearance began.[339]

4. Important natural sources of organochlorine compounds

Some aspects of the organic chemistry of chlorine occurring naturally to have been subjected to particular scrutiny are reviewed in this section. Much of this work has been driven by the need to understand the impact of some industrial processes which directly or indirectly release chlorinated organics into the environment. While potentially hazardous releases of any man-made chemical should be avoided, the formation (and destruction) through natural processes of such materials should provide evidence-based targets for future environmental quality standards as well as insights on which to base approaches for the remediation of polluted sites.

4.1 Chloroalkanes from marine sources

The detection of low molecular weight halocarbons in sea water may signify either a pollution source or a natural source. Air–sea exchange may lead to loss to or pick up from the atmosphere. Oceanic and atmospheric transport will globally distribute such compounds. Transformation and degradation, both biotic and abiotic, can be also expected. Early work on this topic has been summarised by Fogelqvist[414] and Fabian.[415]

The oceans are important sources (as well as sinks[416]) of polyhalogenated alkanes.[417–419] Even algal communities found under polar ice shelves generate these compounds in significant quantities.[420,421] Evidence suggests that chlorinated products may be formed directly but, in addition, chemical exchange between biogenically produced brominated and iodinated materials and chloride ion is also possible. Lovelock first suggested that the ocean was a major source of chloromethane.[52,422–424] Manley and Dastoor reported,[425] from both field and laboratory culture studies, that CH_3Cl, CH_3Br and CH_3I formation is associated with the giant kelp, *Macrocystis*, preferring a kelp-metabolism source rather than one involving 'epiphytes', *i.e.*, algae or bacteria associated with the seaweed. However, they concluded that chloromethane is not formed as a consequence of the known abiotic halogen exchange reaction with iodomethane.[310–314] Further studies have investigated Arctic[426–428] and Antarctic[426,429–432] red, brown and green macroalgae. Antarctic macroalgae show[429] 10–50 fold lower rates of release of MeCl (34.7 pmol g^{-1} (wet algal weight)[9] per day) MeBr (1.98) and MeI (1.68) compared with temperate species. Interestingly, among the several brominated compounds produced in significant quantities is 1,2-dibromoethane,[426,431] a compound also detected in Arctic ice pools.[317] While variation in light conditions influenced the formation and release of 12 volatile halogenated compounds from four species of Antarctic macroalgae, including chloromethane, no clear relationships could be delineated.[430] Pedersén *et al.*[433] have related halocarbon production to illumination and the presence of hydrogen peroxide and propose that these products are formed in the scavenging of H_2O_2 and could possibly simply be secondary products resulting from oxidative stress. Release of halogenated compounds was found to occur from all parts of the thallus of a series of 28 Antarctic macroalga.[431] From more detailed studies on 6 species, it was observed that the highest rates of production came from species with highest surface-to-volume ratio, indicating the formation of volatile halogenated organic compounds in photosynthetically- and metabolically active cortex (surface-located) cells. Brominating and iodinating activity was found[432] in 18 cultivated species of red, brown, and green macroalgae from the Antarctic. Chlorinating activity was detected in only the red alga, *Plocamium cartilageneum.* Brominating activity was found[428] in the blade only, while iodinating activity arose in the whole thallus of Arctic macroalgae. No evidence for chlorinating activity was found. Because estimates of chloromethane productivity of seaweeds fall far short of the proposed total oceanic source, attention has also been focussed on phytoplankton as sources of haloorganics in general[434] and chloromethane in particular, with Tait and Moore providing the first evidence of MeCl production associated with phytoplankton cultures.[435] Seven species of phytoplankton (including cold- and warm-water organisms) were found to produce MeCl and to continue to do so after cell death. Formation of MeCl, MeBr and MeI by phytoplankton under axenic conditions has now been confirmed by Scarratt and Moore.[436,437] However, direct measurements of the chloromethane concentration in sea water (and a recent determination of the Henry's Law constant for MeCl[319]) suggest that the contribution to global oceanic chloromethane production from this source is insignificant,[438] with the net flux estimated to be $(0.3–0.4) \times 10^6$ t per year.[319] A similar conclusion has been arrived at independently for iodomethane production.[439]

Variations in the chloromethane concentrations and partial pressures in waters of the NW Atlantic and Pacific Oceans can be accounted for by variations in sea-surface temperature, with warmer waters all consistently supersaturated. However, there was no correlation[440] between chloromethane concentrations and the presence of chlorophyll *a* (an indicator of biological activity and biomass productivity; see for example ref. 441). For bromethane, similar studies suggest, for waters of the Labrador Sea, that a biological consumption process is likely.[442] Measurements of negative saturation anomalies for bromethane in the Southern Ocean point to a similar sink for this compound[443] (see also ref. 444). Happell and Wallace[445] conclude that photochemical production of iodomethane is the dominant source in the open ocean.

Bromoform has a natural flux of *ca*. 10^6 t per year and its marine origins have been extensively studied.[420, 446–448] Chemical exchange to give $CHClBr_2$, $CHCl_2Br$ and $CHCl_3$ is possible, though in a study of volatiles produced in beds of *Laminaria digitata* off the west coast of Scotland, Nightingale *et al.*[449] confirmed the *in situ* production of haloorganics (CH_3I, CH_2Br_2, $CHBr_3$, $CHBr_2Cl$, $CHBrCl_2$, $CHCl_3$). The authors do not favour formation of these compounds by release of HOBr into seawater and subsequent reaction. Release rates can be influenced by partial dessication, light availability, tissue age, tissue wounding and grazing. No CCl_4, C_2Cl_4 or C_2HCl_3 was detected. The authors suggest that chloroform can be produced directly in the presence of a chloroperoxidase. D-Mannitol has been proposed as a possible precursor to haloform formation from marine algal byproducts.[450]

Walter and Ballschmiter have shown that when commercial chloroperoxidase (not of marine origin) and biogenic carbonyl compounds are incubated together with chloride, bromide or sea salt as halogen source, a variety of polyhalogenated methanes and acetones are produced.[451] Related studies on acetic acid/KBr/chloroperoxidase gave $CHBr_3$ as the main product and $CHBr_2Cl$ and $CHCl_2CHCl_2$ as by-products.[452] The chlorinated products were believed to have arisen from the 500 μg g^{-1} of Cl^- in the KBr reagent. Interestingly, Urhahn and Ballschmiter report[453] that when methionine methyl sulfonium chloride, $[(HO_2C)CH(NH_2)CH_2CH_2SMe_2]^+Cl^-$, was incubated with commercial chloroperoxidase, halide ion and hydrogen peroxide only the monohalomethanes were formed in high yield, whereas substrates with carbonyl- and sulfur-activated methyl groups, $–C(O)CH_3$, $–S(O)_nCH_3$, $n = 0, 1, 2$, gave di- and trihalomethanes and no monohalomethanes. Interestingly, amino acids and natural peptides produce dihalogenated acetonitriles, $CHCl_2CN$ (see also ref. 454) or $CHBr_2CN$ (characterised by GC retention times compared with reference compounds), materials already identified as being produced during deliberate chlorination of natural waters, and other as yet uncharacterised compounds. The authors suggest that halogenated nitriles may be ubiquitous in the natural environment. Biogenic formation of monohalomethanes appears to proceed *via* a metabolic pathway not involving the haloperoxidases.

4.2 Chlorinated acetic acids

Nothing exemplifies better the uncertainties (and the associated controversy) surrounding the origins of chlorinated organic compounds found in the environment than the case of the chloroacetic acids, particularly trichloroacetic acid (TCA) which was used as a herbicide for many years though its use is now regulated. On the basis of a half-life for biodegradation in soil estimated[455] to be between 14 and 90 days, trichloroacetic acid is not expected to accumulate in soil. Because of their low Henry's Law constants (expressed as atm M^{-1}),[456] chloroacetic acids formed in atmospheric processes will be very efficiently scavenged by precipitation and may be introduced into the soil by this pathway. However, concentrations of TCA found in soil[457] cannot be accounted for solely by that deposited in precipitation, pointing to natural sources in the soil. Partitioning from water to air can be considered negligible, resulting in different distributions in and transport between environmental compartments of chlorinated acetic acids compared with those for weakly dipolar low molecular weight chlorinated organics.

The ubiquitous presence of chlorinated acetic acids, particularly trichloroacetic acid, in precipitation thus points to an atmospheric source, possibly from the degradation of volatile organochlorine compounds. The detection of TCA in arboreal lichens on conifers was also ascribed to an atmospheric source. Concern has arisen because the presence of chlorinated acetic acids has been associated with tree damage in forests.[458–463] While haloacetic acids are demonstrably phytotoxic at high concentrations, others remain sceptical that, at the concentrations typically detected in rainfall and surface waters, they are the prime cause of forest decline. For instance, Finnish workers have undertaken studies on germination, growth and related studies on pine seedlings.[464–467] Concentrations of TCA in conifer needles taken from rural forests of northern Finland,[465] which vary between 1–180 μg kg^{-1}, are similar to those in needles taken from the relatively more polluted areas in central Europe.[468] Other studies show that Scots pine seedlings[464] take up TCA both *via* the needle surface and the roots. In exposure studies,[467] repeated application of TCA over two simulated growing seasons *via* either the root or the needles of pine seedlings at concentrations higher than those found in rain and soil water resulted in no visible symptoms of stress. However, a consequence of this exposure was the metabolic breakdown of TCA and the observation of enhanced activity of enzymes in the pine needles associated with detoxification processes.

The proposition that chlorinated acetic acids (and some carbon tetrachloride) arise primarily from the degradation of synthetic chlorinated solvents, such as perchloroethylene, trichloroethylene and 1,1,1-trichloroethane in the troposphere has been widely repeated.[460,461] Certainly, the detection[462] of locally high concentrations of trichloroacetic acid in pine needles taken from 13 sites in the catchment area of the Caspian Sea has been linked with inputs of perchloroethylene of an industrial origin. However, the general presumption that TCA in vegetation or precipitation in remote regions arises solely or predominantly from anthropogenic precursors has only more recently been challenged,[468,469] opening up a fierce debate.[470] This has arisen as a consequence of better understanding of the atmospheric chemistry of these products and evidence to suggest that some of the chlorinated solvents may themselves have natural sources. 1,1,1-Trichloroethane, which has no significant natural sources (though some may be produced in biomass burning[62]), is believed by Jordan and Frank[470] to be the prime source of atmospheric TCA, arising from the oxidation in cloud water of chloral generated by photo-oxidation of 1,1,1-trichloroethane. However, Hoekstra and Juuti[470] have challenged this view citing estimates[471] that only 0.06% 1,1,1-trichloroethane degrades in the atmosphere to give TCA *via* formation of chloral, despite the dominant importance of chloral as a primary degradation product. Franklin and Sidebottom[472] suggest that only 1.6% of chloral is taken up by clouds. Assuming complete conversion of all chloral hydrate in cloud water to TCA, *e.g.* by processes analogous to those known to convert formaldehyde hydrate to formic acid[473] leads to estimates of TCA concentrations in precipitation[472] of *ca.* 20 ng L^{-1} (based on 1,1,1-trichloroethane levels in the atmosphere in the early 1990s). These levels are *ca.* 10 times lower than those measured in central Europe between 1991 and 1997.

With atmospheric lifetimes of 19 weeks and 6.5 days respectively, for C_2Cl_4 and C_2HCl_3, most of these chlorinated olefins will be degraded in the troposphere and little transported to the stratosphere. (Degradation in the stratosphere is likely to lead to phosgene stable enough to be transported to the troposphere and hydrolysed.[474,475]) It is thus important to know the relative contributions of the different pathways and the identity of intermediates and final products associated with the atmospheric degradation of unsaturated chlorinated organics such as C_2Cl_4 and C_2HCl_3. See ref. 476 for a review on the atmospheric fate of C_2Cl_4. A particular difficulty has been applying understanding of oxidation processes under laboratory conditions to the circumstances of the atmosphere. Laboratory studies on the free-radical oxidation of C_2Cl_4 and C_2HCl_3 show that it is initiated by chlorine-atom addition, giving dichloroacetyl chloride and trichloracetyl chloride as the main products, respectively (hydrolysis of which leads to DCA and TCA). However, atmospheric degradation of organic compounds is believed to be dominated by reactions with hydroxyl radicals. On the other hand, the rate constant for chlorine addition to C_2Cl_4 is *ca.* 300-fold larger than that for the addition of OH.[476] (The critical ratio of chlorine to hydroxyl addition rates to C_2HCl_3 is only 30.) The importance of these two pathways, eqns. (17) and (18), to chloroacetic acid formation will thus depend on the relative concentrations of $Cl^\bullet$ and $OH^\bullet$ in the atmosphere and on the nature of the products arising from the pathway initiated by hydroxyl addition.

$$CCl_2{=}CCl_2 + Cl^\bullet \rightarrow CCl_3CCl_2^\bullet \qquad (17)$$

$$CCl_2{=}CCl_2 + OH^\bullet \rightarrow HOCCl_2CCl_2^\bullet \qquad (18)$$

Hithero, chlorine atoms have not been considered important in atmospheric oxidation processes, a conclusion that is being reconsidered in the light of recent observations summarised in Section 2.5. Franklin and Sidebottom,[472] using published rate data and averaged $[OH^\bullet]$ and $[Cl^\bullet]$ of 10^6 and 500 radicals cm^{-3}, respectively, have calculated that 87% of tropospheric C_2Cl_4 reacts with hydroxyl and 13% with chlorine atoms. However, it is recognised that these are rough global averages and that the $[Cl^\bullet]:[OH^\bullet]$ ratio is likely to vary spatially and temporally (see Section 2.5). Franklin and Sidebottom[472] further assumed that only the Cl atom-initiated oxidation pathway leads ultimately to TCA, *via* the intermediate formation of the pentachloroethoxy radical, which breaks down mainly (85%) to $CCl_3C(O)Cl$, the latter being either photolyzed to one-carbon fragments (54%) or taken up by clouds and hydrolyzed to TCA (46%). On this basis, Franklin and Sidebottom[472] have estimated a TCA yield from C_2Cl_4 of *ca.* 5%, a value with considerable uncertainty, though one which converts[472] into TCA concentrations in European precipitation of *ca.* 120 ng L^{-1}, similar to those observed. (Oxidation of C_2Cl_4 and C_2HCl_3 initiated by hydroxyl radicals also yields the two acyl chlorides, $CCl_3C(O)Cl$ and $CHCl_2C(O)Cl$ but, importantly, when carried out in the presence of a scavenger for chlorine atoms, such as ethane, their formation is greatly reduced.[477] In systems confirmed to be free of chlorine atoms, the formation of C_2 products of any sort is negligible.[478,479] The quantification of the atmospheric concentration of chlorine atoms and their spatial and temporal variation thus assumes additional significance.)

Global budget analyses for C_2Cl_4[61,355] remain tentative associated with uncertainties in the source data. On the other hand, one might expect the relative concentrations of TCA measured in the northern and southern hemispheres to reflect the 6 : 1 ratio of the average concentrations of C_2Cl_4 measured[480] in the two hemispheres. Franklin and Sidebottom[472] have estimated TCA concentrations in precipitation (arising from a combination of 1,1,1-trichloroethane and perchloroethylene degradation) to be 57 and 19 ng L^{-1} in the Arctic and Antarctic, respectively, whereas the observed levels for the Arctic and Antarctic[481–484] are in the ranges <5–53 and 22–348 ng L^{-1}, respectively.

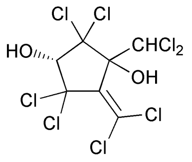
The abundances of C_2Cl_4 and C_2HCl_3 themselves, the putative precursors to TCA and DCA in the remote marine atmosphere, have been the subject of a number of analytical[480,485] and modelling[485,486] studies. From an assessment of known industrial emissions of C_2Cl_4 and C_2HCl_3, significant natural fluxes of these materials of the order of 50×10^3 and 1.3×10^6 t per year, respectively, have been suggested,[486] particularly in the southern hemisphere where anthropogenic emissions are low. For the suggestion of natural sources to be wrong, either there are major unknown industrial sources in the southern hemisphere, the rate of atmospheric degradation is incorrect or the analytical and inventory data are incorrect. While none of these is thought probable, it is still not entirely clear what the additional sources of these materials may be. For instance, VOC emissions from coal-fired power stations are reported to include C_2Cl_4.[487] There is also evidence of oversaturation of remote ocean water in C_2Cl_4 and C_2HCl_3 [61] which may be indicative of a marine source (though, alternatively, this may simply indicate a water mass previously equilibrated with atmospheric C_2Cl_4 and C_2HCl_3 at a lower temperature). Abrahamsson's observations of significant C_2Cl_4 and C_2HCl_3 production by marine macroalgae[349–351] suffer because of a failure unequivocally to identify these products. Furthermore, attempts to reproduce[353] or extend[352] the observations (using cultured algae rather than from field studies[351]) using GC mass spectrometry to characterise these products have been unsuccessful. On the other hand, it is known that algal species sampled from one site can produce a different range of halometabolites from the identical species sampled from another site. See for example ref. 264.

The detection of chloroacetic acids in ancient ice[481–484] from the Arctic and Antarctic and from an ice core dated *ca.* 1900 from an alpine glacier (100 ± 40 ng L^{-1}) suggests that sources of these materials, possibly of geological origin,[482] were available before the development of the modern chlorine industry. Grimvall and colleagues have shown[488,489] that the 1–30 μg of organohalogens (AOX, expressed as Cl^-) per L of rain or snow from urban and rural sources in Poland, Germany and Sweden contain several different types of compounds, including polar non-volatile, non-polar semi-volatile and very volatile compounds whose distribution in the samples is not site-specific. Specific compounds, such as PCBs and chlorine-containing pesticides, generally represent only a small fraction of the organic material detected. Up to 20% of the AOX is associated with chlorinated acetic acids. Using atomic emission (element-specific) detection methodology and by concentrating the organohalogens by rotary evaporation, Grimvall *et al*. have sought to characterise some of the unknown halogenated material.[488,489] Only two additional materials were characterised, namely 1,4-dichlorobenzene and tris(2-chloroethyl)-phosphate. The results suggest that the AOX in precipitation arises to only a minor degree from the presence of volatile and readily extractable organohalogens. The difficulty in characterising the medium molecular weight organohalogen bases arises from their alkaline lability.

In addition to its ubiquitous presence in precipitation, there is now evidence to suggest that soil may be an additional natural source of trichloroacetic acid.[457,490–493] In laboratory studies, Hoekstra and de Leer[457,490,491] have found that, in the presence of chloroperoxidase, humic acid reacts with chloride ion and hydrogen peroxide to generate both chloroform and di- and trichloroacetic acids. In analytical studies on the soil content of TCA and soil air content of chloroform and the solvents C_2Cl_4, C_2HCl_3 and 1,1,1-trichloroethane in different soils, Hoekstra *et al*.[492] have shown that TCA concentrations in soil are not significantly associated with the soil air concentrations of its putative precursors, C_2Cl_4, C_2HCl_3 or 1,1,1-trichloroethane. However, a statistically significant positive correlation was seen between the incidence of chloroform and that of TCA. Chemical decarboxylation of TCA to chloroform under soil conditions is expected to be very slow, suggesting the latter does not arise simply from the former. Haiber *et al*.[493] have carried out similar experiments, incubating humic acid and a range of naturally occurring carboxylic acids (acetic, malic, lactic, citric) with chloride ion and hydrogen peroxide, with and without chloroperoxidase (from the fungus *Caldariomyces fumago*), and confirmed that TCA and DCA, as well as chloroform and chlorinated acetones, are formed. Haiber *et al.* also report the surprising formation of TCA even without added chloroperoxidase, most notably with humic acid. They find also that TCA rapidly became bound, either physically or chemically, to humic acid suggesting that, in some circumstances, an inability to detect TCA may not be evidence of its non-formation. The TCA detected in rainwater which had been allowed to trickle through soil from one site showed seasonal variations, being lower in November/December (<100 ng L^{-1}) and higher in June (*ca.* 2000 ng L^{-1}), a trend observed earlier by Fillibeck *et al*.[494] and also by Reimann *et al*.[495] However, no such trend was seen in rainwater from a second site. It was also shown that TCA-containing rain water allowed to trickle through soil prior to collection lost 80–90% of the TCA. High levels of TCA (300–1000 ng L^{-1}) found in bog waters (containing high levels of dissolved organic carbon, including humic materials) was unexpected, but pointed to a net production of TCA in such media, possibly associated with their relatively acidic pH (pH 4). Chlorobenzoic acids have also been found in bog water, with the concentration of 2,4-dichlorobenzoic acid being correlated with that of TCA, suggesting a common natural source[496] rather than one from degradation of polychlorinated biphenyls.

4.3 Fungal metabolites

Fungi play an important role in soil chemistry, with the basidiomycetes responsible for breaking down lignocellulosic components of wood and other vegetable matter. In so doing, these fungi produce and transform a diverse a range of chlorine- (and halogen-) containing natural products,[497] many in prodigious quantities and as a very high proportion of biomass dry-weight, much of it difficult-to-characterise material analyzed as AOX, adsorbable organic halogen. Chlorinated natural products include C_1 chlorocarbons, such as chloromethane and chloroform,[346] a wide range of chlorinated phenols, anilines, anisoles (see also refs. 498, 499) and related aromatic aldehydes, as well as more complex structures, such as periconin B **47**, isolated from the fungal pathogen, *Periconia circinata*.[295] These materials are not surveyed comprehensively; the purpose of this section is to highlight the contribution that these organisms (and, with algae, as lichens) make to the natural organic cycle of chlorine and to underline, once more, their importance as major sources of materials hitherto thought solely to be man-made pollutants. It was from a lichen (a ‘symbiont’ of a fungus and an alga) that diploicin **14** was first isolated and characterised over 90 years ago. Since then, fungi have been the sources of many important early antibiotics, produced industrially by fermentation, such as griseofulvin **18**, chloramphenicol **62**, aureomycin **63** and caldariomycin **19**. Some products of fungal origin are surprisingly highly chlorinated, with **79**, $C_7H_4Cl_8O_2$, isolated from the fungus *Mollisia ventosa*, containing 70.3% by weight of chlorine.[268,269] 3,5-Dichlorohexanophenone **75**, produced by the slime mould, *Dictyostelium discoideum*,[401] has a quite precise physiological function already discussed in Section 3.4. Drosophilin A **44** a chlorinated antibiotic,[292] and the related tetrachloro-1,4-dimethoxybenzene **80**, are reported to be produced *de novo* by 5 of 92 screened lignolytic fungi[500] (that is, those capable of breaking down the woody component of vegetable matter). Recently two novel chlorine-containing 2,3-dihydro-1-benzoxepins **81** and **82** have been isolated from *Mycena galopus*.[501]



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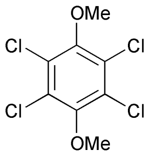

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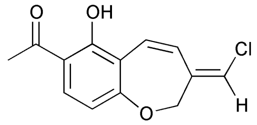

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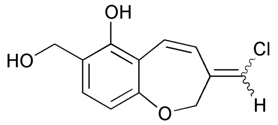

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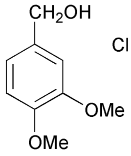

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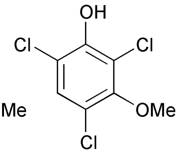

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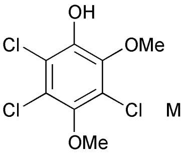

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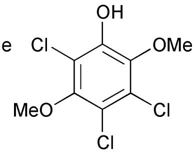

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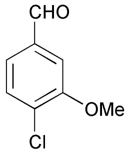

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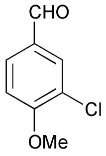

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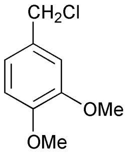

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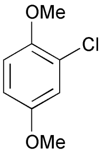

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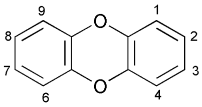

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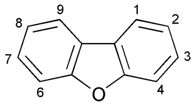

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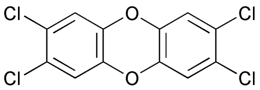

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Renewed attention is being focused on terrestrial fungi, particularly wood-rotting fungi,[410] as possible sources of chloromethane, as a consequence of a conclusion from the recent Reactive Chlorine Emissions Inventory study that the known marine sources of chloromethane cannot account for its global annual production. It was Hutchinson[502,503] who first established that chloromethane could be produced by fungi, and Harper and colleagues who later established it to be a secondary metabolite[339,504] from fungi grown on a range of substrates. Yields of chloromethane based on chloride ion in the growth medium were as high as 90%. Fungal biosynthesis of chloromethane was found to be widespread in a family of white rot fungi, the Hymenochaetacaeae, with 54% of 63 species from 6 different genera releasing chloromethane in the presence of chloride ion. Harper *et al.*[403] also identified methyl esters of benzoic, 2-furoic and salicylic acids amongst volatile products from cultures of *Phellinus pomaceus* and again showed this characteristic to be widespread amongst chloromethane producers (and absent from non-chloromethane producers), suggesting the two processes of ester formation and chloromethane production were associated. Studies[402,405,408,409,505] using deuterium-labelled amino acids, such as L-[methyl-d$_3$]-methionine, $CD_3SCH_2CH_2CH(NH_2)CO_2H$ **83**, indicated that such materials could be precursors to both chloromethane and the methyl esters of benzoic and furoic acids. More importantly, Harper and Hamilton established[402] that methyl ester formation for benzoic acid employed chloromethane as methylating agent and also that other substrates such as phenols could be methylated.[404] Such chloromethane utilization was shown to be widespread even amongst many wood-rotting fungal species which do not release chloromethane during growth, with label-incorporation into veratryl alcohol (3,4-dimethoxybenzyl alcohol **84**, a key secondary metabolite involved in lignin degradation) isolated from cultures of *Phanerochaete chrysosporium* being more efficient in the presence of added CD_3Cl than added CD_3-labelled methionine **83** or CD_3-labelled *S*-adenosylmethionine **83a**, the conventional biological methyl donor.[405,408,409] It was suggested[404] that the participation of chloromethane as a metabolic intermediate in primary fungal metabolism observed in these investigations was the first unequivocal evidence to support the contention by Neidleman[506,507] that some halometabolites may have roles as transient intermediates in the biosynthesis of halogenated products. (Biochemical methylation of chloride ion is discussed further in Section 5.1.)

The ubiquity of natural halogenated organic production (measured using the parameter AOX, adsorbable organic halide) from basidiomycetes was shown from a study of 191 fungal strains, many important ecologically, 50% of which produced AOX when grown on a specific medium.[508,509] Production of halogenated species from the genera *Hypholoma*, *Mycena* and *Bjerkandera* showed specific AOX production in the range 1–31 g AOX kg^{-1} dry weight of mycelial biomass. Cultivation on natural lignocellulosic substrates such as forest litter also led to AOX formation.

Over 60 low molecular weight, mostly chlorine-containing, aromatic compounds have now been isolated from fungi and shown to be widespread in the natural environment.[497,510] Among the characterized species are **77**, **78**, **84**, 2,4,6-trichloro-3-methoxyphenol **85**,[511] 3,5,6-trichloro-2,4-dimethoxyphenol **86**,[511] 3,4,6-trichloro-2,5-dimethoxyphenol **87**,[511] as well as **44**, **88** and **89** reported from the early studies by Anchel[292] and Thaller and Turner.[512] The white-rot fungus *Bjerkandera* sp. BOS55 has recently[513] been shown to produce deuterated veratryl chloride (3,4-dimethoxybenzyl chloride **90**) from deuterated benzoic acid, the first example of a biogenic benzyl chloride. While chloroperoxidases have been isolated from several fungi (see Section 5.1), the biosynthetic routes to these products remain fully to be established, though *de novo* production has been established in some instances. Very recent work on *Hypholoma fasciculare* shows that AOX production takes place during the transition between the primary and secondary metabolic phases of the growth cycle of the fungus, with maximum AOX production rates of 0.63–3.23 mg AOX g^{-1} dry mycelium per day and final yields ranged from 0.88–1.50% of dry weight of mycelium on five different substrates including natural woody substrates. The composition of AOX changes with time, with initially most of the AOX accounted for by 3,5-dichloro-*p*-anisyl alcohol **8** which, after prolonged incubation, was converted mainly into 3,5-dichloro-*p*-anisic acid **78** or unidentifed organohalogens, depending on the nitrogen content of the medium.[45,514] These observations, with other data, led to estimates that this species alone contributes, where found, *ca*. 110 g of AOX per hectare per year.

Studies by de Jong, Field *et al.* have established that chlorinated anisyl metabolites have a physiological role in lignin degradation, serving as substrates for aryl alcohol oxidases involved in extracellular hydrogen peroxide production.[412,413] The oxidases have a much higher affinity for chlorinated anisyl alcohols, such as **8**, than related non-halogenated secondary metabolites (*e.g.* veratryl alcohol), oxidising the alcohols to the corresponding aldehyde (*e.g.* **77**) (which is subsequently rereduced to the alcohol), reducing dioxygen to H_2O_2 as they do so. Hydrogen peroxide is a required co-substrate for exocellular peroxidases which are key to the degradation of lignin. The chlorinated substrates are also thought to be less susceptible to lignin-peroxidase-mediated oxidation than the non-chlorine-containing analogues, possibly because of the effect of the chlorine substituent on relevant redox potentials. 2-chloro-1,4-dimethoxybenzene **91** can also mediate the oxidations by lignin peroxidase, since the oxidations studied[515] did not proceed in the absence of the secondary metabolite.

That fungi can bring about a series of chlorinations involving biochemical redox processes and the fact that such materials are found not to accumulate in the environment where they are formed suggests that processes of dechlorination have also evolved. Biotransformation of chlorinated soil components leading to complete mineralization or to incorporation into soil humus[497] is discussed in Section 5.2. Such chlorinated components may, of course, be either natural or man-made.

4.4 Chlorinated organics in soil, groundwater and freshwater sediment

While the relevant data remain limited, the greatest quantity and variety of chlorinated organics are likely to be found in the marine environment. On the other hand, we also know that the terrestrial and non-marine aquatic environment receives significant fluxes of inorganic chloride from the deposition of sea-salt aerosol, in precipitation (also from sea-salt aerosol and from emissions of HCl from volcanoes and combustion processes, as well as from the decomposition of man-made organochlorine compounds) and from weathering processes of rocks. However, the terrestrial biogeochemistry of chlorine, and its cycling between soil, water, biota and dead organic matter, is a relatively unresearched area. See ref. 85 for a recent review.

The lower concentrations of chloride in fresh water and soil might point to the unimportance of natural terrestrial chlorination as a source of organochlorine compounds and explain the only relatively recent recognition of their presence (surprising, perhaps, when one considers the very many studies on the presence of man-made materials). In fact, the detection of chlorinated organics, including chloroform, chlorinated phenols and the potent mutagen, MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone **60**[516,517]) in drinking water has been associated with the extensive use of chlorine for the disinfection of drinking water. However, there are now a number of studies which demonstrate that natural chlorination leading to chloroform,[518–520] trichloroacetic acid (described in detail in Section 4.2)[457,520] and chlorinated phenols and benzoic acids,[521] is widespread. Their presence in soils and groundwater thus arises not only as a consequence of water disinfection using chlorine.[522] Brominated disinfection byproducts may arise in a similar fashion.[454,518,523] (Interestingly, dibromoacetonitrile may be detected as the only brominated compound in the treatment of (bromide-containing) water with ozone,[454] the $CHBr_2CN$ being present also, at lower concentrations, in untreated water.) The important question which arises, namely, to distinguish between the natural and anthropogenic origin of a chlorinated compound, is discussed in Section 7.

Terrestrial biota, such as fungi, plants, animals and insects, are also now known to be *de novo* producers of low molecular weight chloroorganics. Important chlorine-containing antibiotics have long been produced on the industrial scale (albeit *in vitro*) by bacteria originally isolated from soil. A species of freshwater mussel itself appears to produce or accumulate chlorinated lipid fatty acids in a non-polluted environment similar to those it accumulates from a polluted one.[362] We know also that the burden of chlorinated organics in the river Rhine, originally believed to have been derived solely from the pulp and paper industry, includes[368,369] a significant (*ca*. 50%) natural source.

This section reviews additional evidence that higher molecular weight organic matter found in soil, groundwater[524] and sediment has a significant organochlorine content of natural origin.[525–530] The focus will be on the sources, nature and transformations of so-called 'AOX', adsorbable organic halogen, a standard analytical parameter[531–533] used to characterise the complex high molecular weight involatile halogenated organic content of environmental waters, particularly that derived from dead organic material. The latter is made up of fulvic and humic substances, the extremely complex organic structures produced during the breakdown in the soil of organic matter of plant and animal origin.[371] Such material is difficult to isolate, analyse and study.

Three different Swedish groundwaters,[531] estimated from ^{14}C measurements on the fulvic acid content to be between 1300 and 5200 years old, hence (within the uncertainties of the measurements) formed well before industrial use of chlorine and its compounds began, were shown to contain 230–370 μg AOX g^{-1} organic matter.[531] AOX measurements on a raised bog in a remote region of Sweden suggest the presence of amounts of AOX *ca*. 300 larger than expected from annual deposition of organochlorine pollutants. The presence[529] of AOX (1–80 $\mu g\ L^{-1}$) in all but one groundwater samples drawn from 145 wells in Denmark suggests the ubiquitous presence of organohalogen compounds.

Related studies of sediments (from rivers, reservoirs and lakes, as well as from the sea),[534–537] of peat, lignite, bituminous coal and anthracite[534] and of a soil humic acid[538] all reveal the presence of significant amounts of organohalogen compounds believed to be of natural, and sometimes ancient,[534,536] origin. Studies have also been undertaken to characterise the processes in soil which generate organically bound halogens *in situ*. Particular attention[539] has been given to coniferous forest soil, with the concentrations of organohalogens (μg Cl g^{-1} soil) decreasing with increasing depth (associated with a decline in organic matter with depth) though the proportion of organic chlorine to organic carbon (mg $Cl_{org}\ g^{-1}\ C_{org}$) increases with depth. Studies[539] of leaf-litter from Norway spruce showed a net production of organically bound halogen during leaf-litter decomposition. Significantly, both incorporation of inorganic chloride into organic matter as well as its release from organic matter occurred during decomposition. In addition to the organohalogen material generated by these processes, studies of seasonal effects, wind-direction, collector position on the deposition of organics in throughfall onto the spruce forest floor, suggest that both organic carbon and organic halogen may arise from leaching from the tree canopy.[539–542] Significantly, the pool of organically bound chlorine in the soil of the spruce forest floor was estimated to be 630 kg ha^{-1}, with an accumulation of 0.35 kg ha^{-1} per year per year from litterfall and loss by leaching of 0.63 kg ha^{-1} per year.[540,541] Contributions from throughfall were estimated to be 0.38 kg ha^{-1} per year and net formation within the soil 0.36 kg ha^{-1} per year.[540,541] (Chlorinated organics in precipitation are dealt with in Section 4.2.) Attempts to characterise these complex materials have shown only that chlorinated aromatic moieties are present (being similar to those produced during bleached kraft mill effluent).[543–547] The similarity between these products and the lignin-derived chlorinated metabolites from wood-rotting fungi previously discussed in Section 3.4 is striking.

If, as seems likely, the processes of chlorinated organic production in soils are widespread, then massive quantities of organochlorines are likely to be present in soil, with estimates as high as 10^9 t having been made.[257] The nature of the sorption of such materials (and related anthropogenic pollutants) by sediments and soils and the processes of desorption and mobilisation (important for discussions of bioavailability and processes of attenuation) are complex, not well understood and difficult to predict.[548] These soil components may be linked more generally to the cycling of organic matter in the soil and thus to the carbon cycle. It is hoped that by understanding the biogeochemical cycles of these naturally-occurring organochlorine compounds that the breakdown and fate of anthropogenic compounds, their environmental impact and approaches to the remediation of contaminated sites can be better understood. At present, the mechanisms by which they are formed are not well understood, though chloroperoxidase-type enzymes, capable of chlorinating fulvic acid, are present in soils,[376,549,550] including spruce forest soil.[550] In addition to the characterisation of products formed from chlorination of humic materials,[528,530,551] studies of the chlorination of resorcinol,[552] chosen as a surrogate for humic acids, has established an unequivocal link, using isotopic labelling, between structural units present in humic materials, and chloroform, trichloroacetic acid and other chlorinated disinfection by-products. Bearing in mind the similarities between such natural processes of chlorination and those arising from water disinfection using molecular chlorine, the possible natural formation of the potent mutagen, MX **60**, cannot be ruled out.

Our ability to establish the precise origin of chlorinated products in soil, and to apportion the sources between natural and anthropogenic is complicated by the fact that low molecular weight organics (chlorinated and non-chlorinated; anthropogenic and naturally produced) may be incorporated into soil humus during humification.[378–380] Such processes have been considered as a means of sequestering chlorinated phenols and rendering them unavailable, though the possibility that 2,4-dichlorophenol incorporated into humic acid may subsequently be released has also been investigated.[381] Both 2-chlorophenol and 4-chlorophenol are incorporated into humic acids in the presence of horseradish peroxidase,[381,382] suggesting one mechanism by which a chlorine-containing humic acid might be formed. Direct chlorination of a humic acid, mediated by a chloroperoxidase[553] has been described and haloperoxidase-type activity in soil has been confirmed.[549]

4.5 'Dioxin'

Of the several groups of chlorinated materials found in the environment, none has given rise to more public concern than 'dioxin'. So-called dioxin, in fact a collection of 210 compounds consisting of two groups of chlorine-containing tricyclic aromatic compounds, derivatives of dibenzo-*p*-dioxin **92** (the 75 polychlorinated dibenzo-*p*-dioxins (PCDDs)) and of dibenzofuran **93** (the 135 polychlorinated dibenzofurans

(PCDFs)) are collectively better described by the shorthand PCDD/Fs.[554–556] PCDDs and PCDFs display a range of toxicities, with only 17 (those with chlorines in the 2, 3, 7 and 8 positions) of the 210 compounds (‘congeners’) being considered toxic. The congener with the greatest toxic potency is 2,3,7,8-TetraCDD **94**. To permit the characterisation of risk associated with possible exposure to mixtures of PCDD/F congeners of different toxicities (and in the absence of full toxicity data for many congeners), the 17 toxic congeners have been assigned internationally accepted Toxic Equivalent Factors (TEFs).[557] On this basis, 2,3,7,8-TetraCDD has been assigned a value of 1, two other congeners a value of 0.5, eight a value of 0.1, one of 0.05, three of 0.01 and two of 0.001. Such factors can then convert analytical data for the individual PCDDs and PCDFs in a sample containing several congeners into a single parameter, the toxic equivalent (TEQ) amount of 2,3,7,8-TetraCDD.

While the effects of acute exposure to high levels of certain members of the series are unpleasant and the consequences of long term exposure to ambient levels need to be understood, nevertheless, some of the complex physiological effects arising from exposure to other members may be counter-intuitive in that there may be potentially beneficial as well as potentially harmful consequences (though, of course, this would be no justification for failing to control exposure).[558–562] The assessment of the totality of relevant and reliable toxicological, metabolic, physiological and epidemiological data required to give a balanced appreciation of the risks (particularly the cancer risks in humans) associated with exposure to PCDD/Fs has not been without its difficulties. (See, for example, refs. 563 and 564.)

PCDDs and PCDFs are formed as unwanted (and unintentional) by-products in a variety of chemical processes, such as in the production chlorinated phenols and in pulp-bleaching. However, chemicals production is a relatively unimportant source of dioxins emitted to the environment (see Table 3, taken from ref. 565). Interestingly, analysis of virgin PVC resin from suspension polymerisation shows it to contain no PCDD/Fs at or above the detection limit of 1 part in 10^{12} (ppt).[566] Incineration and combustion of chlorinated organics, or even of chlorine-free organics in the presence of chloride ion,[567–569] may lead to low levels of PCDDs and PCDFs. For example, in a recent study,[570] increased levels of PCDD/Fs have been detected in the environment in the UK in the period following the 5th November, traditionally a date on which the Gunpowder Plot of 1605 is commemorated by bonfires and fireworks. Recent work has centred on the study of the fireworks themselves.[571] Natural combustion processes, and some biological processes discussed further below, are also believed to be important historical sources of these products, accounting for their ubiquitous presence in the environment.[572] Recent work has shown a PCDD/F background concentration in the remote marine atmosphere of *ca.* 20 fg m^{-3}.[573] Studies at a semi-rural site in the UK of the seasonal variation of the atmospheric content of PCDD/Fs in air masses of known origin suggest[574] that diffuse combustion-related sources are important in influencing PCDD/F concentrations in ambient air. Attempts to distinguish what might be thought to be ‘natural’ sources from ‘anthropogenic’ sources are fraught with difficulty (for additional discussion on this point, see Section 7). In considering combustion sources, is it, for instance, always possible to distinguish between a natural fire and a man-made one? Fires started by lightning fall into the former category while the burning of biomass as a consequence of traditional ‘slash and burn’ agricultural techniques should be classified as the result of man’s activities, though these are to be further distinguished from industrial operations, such as modern incineration. To establish the origin of PCDD/Fs in combustion products from these different processes we would also need to show whether or not the material had simply been present in the fuel and released as a consequence of its volatilisation. Was this PCDD/F present in the fuel of natural or man-made origin or a mixture of them both? Furthermore, the immediate precursors of PCDD/Fs are thought to be chlorinated phenols, which themselves may have natural or synthetic sources. If some proportion of the dioxins is formed in *de novo* processes from inorganic chloride ion and organic material, what are the origins of these components? Are they entirely ‘natural’ or not? Such questions concerning, for instance, the contribution to PCDD/F burdens from the combustion of wood[575] might include: how much PCDD/F has been deposited on the wood from the atmosphere? Has the wood been treated with chlorine-containing pesticides? What is the chloride content of wood?

Table 3 Estimates of PCDD/F emissions in the UK (g TEQ per year)[565]

Process	1993	1997 Low	1997 High
Coke production	2	2	2
Coal combustion (industrial)	5–67	5	67
Coal combustion (power generation)			
Waste oil combustion	0.8–2.4	0.8	2.4
Wood combustion	1.4–1.9	1.4	1.9
Straw combustion	3.4–10	3.4	10
Tyre combustion	1.7	1.7	1.7
Landfill gas combustion	1.6	5.5	5.5
Sinter plants (4 sites)	29–54	25	30
Iron and steel	3–41	3	41
Non-ferrous metals (1 site)	5–35	29.8	29.8
Cement manufacture (5 sites)	0.2–11	0.29	10.4
Lime manufacture	0.04–2.2	0.04	2.2
Glass manufacture	0.005–0.01	0.005	0.01
Ceramic production	0.02–0.06	0.02	0.06
Halogenated chemicals	0.02	0.02	0.02
Pesticide production	0.1–0.3	0.1	0.3
MSW combustion (14 sites)	460–580	122	199
Chemical waste (10 sites)	1.5–8.7	0.02	8.7
Clinical waste (5 sites)	18–88	0.99	18.3
Sewage sludge (5 sites)	0.7–6	0.001	0.37
Carbon regeneration	0.006	0.006	0.006
Asphalt mixing	1.6	1.6	1.6
Pentachlorophenol in timber processes	0.8	0.8	0.8
Animal carcass incineration		0.001	0.18
Crematoria	1–35	1	35
Domestic wood combustion (clean)	2–18	2	18
Domestic wood combustion (treated)		1	5
Domestic coal combustion	20–34	20	34
Traffic	1–45	1	45
Natural fires (wood)	0.4–12	0.4	12
Fires (accidents)		10	81
TOTAL	560–1100	219	663

In a study undertaken for the US EPA,[576,577] estimates have been made of inorganic, organic and particulate materials emitted during the burning of domestic waste in modified 55 gallon drums or barrels, a practice widespread in the USA. From a public health point of view, probably the most significant observation from this study was the large quantity of benzene emitted (*ca.* 1 g/kg of waste combusted). Some chlorinated organics, including PCDDs and PCDFs, were also detected. Significantly, when the results were compared with the amounts emitted by a typical 200 tons/day municipal solid waste incinerator (MSWI), a **single** typical back-yard barrel fire produced PCDD and PCDF well in excess of that from the MSWI each day.

While it is possible to effect the complete destruction to HCl, CO_2 and H_2O of chlorine-containing organic compounds by thermal oxidation through the proper control of process conditions, PCDDs and PCDFs may reform during the cooling of the exit gases from the reactor, unless the temperature quench rates are sufficiently high and particulates, on the surfaces of which occur the heterogeneous processes of oxychlorination believed to be responsible for reformation, are removed. Recent work[578,579] has concluded that PCDD/F formation occurring in the lower-temperature regime (200–650 °C) proceeds *via* chlorination of (non-chlorinated) dibenzofuran and dibenzo-*p*-dioxin formed at temperatures >650 °C. Careful study of technical data for many incinerator operations has failed to establish a link between the chlorine content of the feed and PCDD/F formation.[580–582] Laboratory studies also confirm that dioxins are combustion products even from fuels devoid of chlorinated organics.[567,569] Thus, for PCDD/Fs potentially to be formed in combustion processes, a source of inorganic chloride, a suitable surface, oxygen and a redox catalyst (such as copper or iron)[583,584] are all that are needed. Indeed, attempts to reduce particulate emissions from diesel engines by the addition of organocopper compounds have been associated with increased PCDD/F emissions.[585] Even the use of copper wire in the classical Beilstein test for testing the presence of halide in organic compounds leads to PCDD/F formation.[586]

There is no doubt that industrial and anthropogenic activity of many kinds has contributed significantly to the burden of PCDD/Fs in the modern environment. Because of their lipophilic nature and persistence, PCDD/F bioaccumulation occurs leading to bioconcentration along the food chain. Much work on the extent and suggested consequences of these processes has been published, though is not reviewed here. However, it is noteworthy that, along with chlorinated organics generally,[29–32] concentrations of PCDD/Fs in various environmental compartments and biota (including the dietary intakes of humans[587]) appear to have peaked in the 1950s, ’60s and ’70s and are now generally on a downward trend.[588–595] Recent analytical studies on breast milk[596] and human blood[597] also show declining trends. Freeze-dried samples of human blood plasma, archived since 1944, have recently been found[598] to contain 55 ppt PCDD/F, a level significantly greater than found today in the USA and Europe. The PCDD congener profile of the blood sample is similar to that of an archived sewage sludge sample from 1933.[599] An interesting recent report[600] suggests, from mass-balance studies of the human dietary PCDD/F intake (mean daily intake 49 pg TEQ per day (range 23–96)) and fecal excretion (mean daily excretion 98 pg TEQ per day (range 40–200)) on 7 male and 7 female adults (aged 24–64 years), that the human body is currently a net emitter of PCDD/Fs. If confirmed, this may arise from the reduction in body burden, consistent with a decreasing intake associated with the observed declining environmental trends.[601] Alternatively, *de novo* formation of PCDD/Fs or biochemical formation from a precursor in the body may be occurring, no longer a proposition without precedent [602,603] (see also Section 5.3). However, an overall picture of sources and sinks for the global burden of PCDD/Fs is still a matter of debate,[604–610] with atmospheric transport and deposition[611–614] of these semi-volatile and hydrophobic materials, particularly in remote non-industrialised areas being of concern.

The PCDD/F content of pre-industrial samples of soil and herbage[589,590] and the associated congener profile (which provide a fingerprint which may be characteristic of the source[615–617]) show that sources were present (albeit at low levels) in the environment before widespread industrial development and the advent of the chlorine-based industry had occurred. In fact, the chlorine industry is only a minor emitter of such products.[608,610] It is also perhaps ironic that the very chlorinated solvents whose elimination is being sought are particularly effective in the removal of PCDD/Fs from clothing during dry-cleaning.[618]

That PCDD/Fs existed in the environment prior to the widespread development of the chloroaromatics and chlorine industry was confirmed by the analysis of a previously unopened bottle of soil collected in 1881 from a controlled long-term agricultural experiment at Rothamsted Experimental Station.[589] The 1881 soil sample contained 0.7 ng of Σ TEQ kg^{-1} soil. Modern soil sampled from the same field plot now contains 1.4 ng of Σ TEQ kg^{-1}, an increase resulting from cumulative atmospheric deposition of PCDD/Fs retained in the surface layers of the soil. Interestingly, the Σ TEQ concentration[589] of archived herbage samples collected year-on-year from Rothamsted between 1980 and 1995 have trended downward by a factor of 3–4, implying a recent decline in the atmospheric deposition of PCDD/Fs and supporting a previously reported[590] longer term decline. (The validity of the experimental procedures employed in these studies has been challenged[604] and defended).[605]

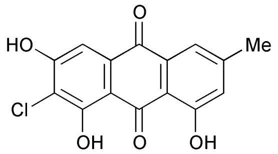
Similar trends have been seen in the temporal record of PCDD/Fs in lake sediments (‘paleolimnology’ or ‘chronostratigraphy’) from a remote lake in north-west Scotland.[615] The contribution of different homologues (congeners containing the same number of chlorine atoms) to overall PCDD/F concentrations has remained broadly similar since the 1800s, dominated by OctaCDD. The relatively minor changes in the homologue profile over time suggest that atmospheric transport and deposition processes may have mixed the inputs from different sources, producing a more uniform profile in the lake sediments. A similar study on dated lake sediments from the Black Forest[592] reveals significant PCDD/F content in sediment layers believed to pre-date the large-scale industrial production of chlorinated organics. Studies on sediment layers from Lake Stechlin in Germany suggest PCDD/F levels increased by a factor of about 100 since the 19th century though have halved since their peak in the 1970s.[593] From measurements in sediments from Großler Arbersee, Germany, Bruckmeier *et al*.[594] show that the sum of TCDD-OCDD and TCDF-OCDF concentrations increase from 996 ng kg^{-1} dry weight (from sediment deposited between 1963–1968) to 1435 (1968–1972), 2049 (1972–1977) and peaking at 2298 (1977–1981) followed by a decline to 1865 (1981–1985) and to 1670 ng kg^{-1} dry weight in the most recent sediment. However, the PCDD temporal pattern differed from that of the PCDFs suggesting possibly different origins. Japanese workers[619] have suggested that PCDDs are present in marine sediments 1–10 million years old. 27 sediment samples from 15 lakes in southern Mississippi are dominated by the presence of OctaCDD and HeptaCDDs.[617,620] These are thought to be of natural origin because the lakes have not been impacted by industrial activity and because the congener profile does not resemble known or likely anthropogenic or technical sources. In particular, a Σ PCDD/Σ PCDF ratio of >100 does not correspond to expectations of a technical source.

Kjeller and Rappe[595] also found PCDDs and PCDFs in a 110 year old core from the Baltic Sea. A sediment core from the northwestern part of the Baltic Proper was sliced into nine dated discs (average age: 1882, 1906, 1922, 1938, 1954, 1962, 1970, 1978 and 1985). Both PCDD/Fs and PCBs were detected in small but significant levels during the period 1882–1962 (total PCDD/F 92–234 pg g^{-1}). The proposed sources are combustion of various natural materials such as coal, wood and peat. Higher PCDD/F and PCB concentrations were found during the period 1970–1985 (total PCDD/Fs 520–1800 pg g^{-1}), this coinciding with a change in PCDD/F congener profiles and isomeric patterns consistent with an anthropogenic origin of the additional material.

While it is reasonable to expect that sewage sludge arising from the treatment of human waste will contain PCDD/Fs (and this topic has been reviewed by Jones and Sewart[621]), it is unexpected to find reports that PCDDs and PCDFs may be formed (or released) during semi-anaerobic treatment of sewage sludge.[599,622–625]

Evidence has also recently begun to emerge, confirmed from a number of independent studies,[625–628] that processes such as composting of organic material may lead to increased concentrations of PCDD/Fs (though another study was inconclusive[629]). A biogenic origin has been proposed[630] for at least some of the PCDD/Fs detected in peat bogs (in New Brunswick, Canada). This has begun to focus attention on possible microbiological and enzymatic processes which might result in the generation of PCDD/Fs. Enzyme mediation of PCDD/F formation has been reported by Rappe *et al.*,[631–633] with evidence for the formation of even the most toxic of congeners, 2,3,7,8-TetraCDD. Carlsen *et al.*[634] have also reported that chlorinated dioxins and furans are formed in the enzymatically mediated chlorination of humic acids, with the highly chlorinated homologues, HeptaCDD, HeptaCDF and OctaCDD, being most abundant. Hemming *et al.*[635] have reported similar findings. In more recent work[636] pentachlorophenol has been found to yield OctaCDD in the presence of horseradish peroxidase though the amounts were reduced in the presence of aromatic carboxylic acids added as surrogates for humic acids. Sediment-associated PCDD/Fs are now believed not to be inert,[386] with OCDD being *peri*-dechlorinated to TCDD and further laterally dechlorinated to 2-MCDD. In studies on a HpCDD, dechlorination was found[637] to be mediated by humic acid, and the humic acid surrogates, catechol and resorcinol.

Perhaps the most convincing evidence that PCDD/Fs may be produced naturally comes from very recent work by Hoekstra *et al.* who have detected the presence of significantly enhanced levels of ^{37}Cl in chlorinated dibenzo-*p*-dioxins and dibenzofurans isolated from the soil of a Douglas fir forest (Speulerbos, The Netherlands) one year after the soil had been treated *in situ* with a solution of sodium chloride-37.[638] The PCDD/Fs are thought to arise from naturally formed chlorophenolic precursors.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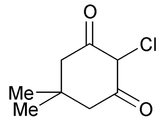
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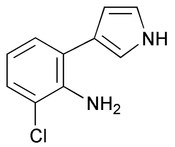
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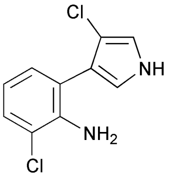
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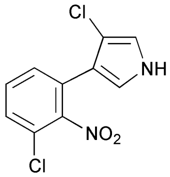
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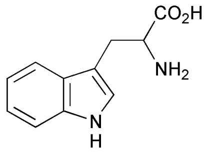
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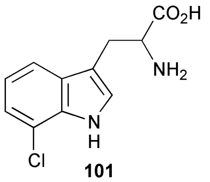
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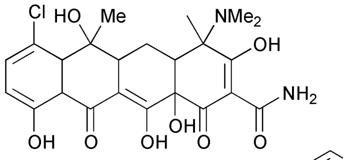
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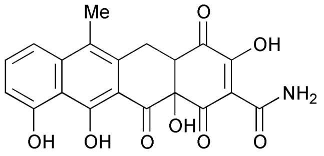
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5. Biochemical chlorination and biodechlorination

The diversity of types and ubiquity of sources of halo- (particularly chloro-) metabolites underlines the biochemical significance of these materials and raises questions regarding the mechanisms, chemical and biochemical, by which they are produced, transformed and degraded. While there have been extensive studies of biological dechlorination, driven by concerns regarding the environmental fate of chlorine-containing pollutants, the related study of biological chlorination (or halogenation) is, relatively, still in its infancy. While this is so, the capabilility to effect biologically mediated chloroorganic formation is likely to be ancient. For instance, 'molecular fossils' of biological lipids characteristic of cyanobacteria, the source of many halometabolites, have recently been isolated from shales estimated to be 2.7 × 10^9 years old.[639] Very few biochemical pathways leading to chlorinated or halogenated metabolites have been fully characterised. However, these topics have recently received a stimulus from the recognition of the potential of haloperoxidases as less-polluting oxidation and halogenating catalysts.[506,640,641]

5.1 Biochlorination

Evidence that many chlorinated organic compounds arise biogenically has arisen from studies of isotopically labelled compounds, such as the use of ^{37}Cl-enriched chloride in the growth medium as well as more detailed studies of biochemical pathways using ^{14}C, ^{13}C and ^{36}Cl-labelling techniques, such as the formation of chlorinated anthraquinones, *e.g.* 7-chloroemodin **95** by the lichen, *Nephroma laevigatum*.[642] However, in general, the understanding of the biochemical mechanisms and the role of chlorinating enzymes leading to them is limited. Early work on biochlorination has been surveyed by Petty,[643] Doonan,[254] Fenical[644] and Neidleman.[506] More recent monographs or reviews have appeared from Neidleman and Geigert,[507] Kirk[645,646] and Geckeler and Eberhardt.[647] The proceedings have also recently been published[648] of the first ever meeting, held in 1996, designed to bring together those studying biohalogenation and those studying dehalogenation.

In their monograph, Neidleman and Geigert[507] identify only one type of halogenating enzyme, the haloperoxidases, which are involved in the general reactions of eqns. (19)–(21), where X$^-$ = chloride, bromide and iodide, with products typical of those involving electrophilic halogen ('X$^+$') with aromatic or olefinic substrates.

$$H_2O_2 + X^- + H^+ = HOX + H_2O \qquad (19)$$

$$HOX + H^+ = H_2OX^+ = H_2O + \text{`}X^+\text{'} \qquad (20)$$

$$\text{substrate} + \text{`}X^+\text{'} = \text{halogenated substrate} \qquad (21)$$

Chloro-, bromo- or iodoperoxidases were discovered only relatively recently[649] and are related to the peroxidases, a class of redox enzymes known since the 19th century. Both groups are ubiquitous,[419,650] being found in bacteria, fungi, lichen, algae and other marine, fresh-water and terrestrial organisms, and are now known to play a central role in the natural formation of organohalogen compounds.

While polyhalogenated methanes and higher alkanes may also be formed by reactions of haloperoxidases,[651] monohalomethanes are believed to be formed microbiologically by a different type of process, involving a net nucleophilic displacement by halide ion,[222,329–331] X$^-$, exemplified by eqn. (22), where LG = a leaving group, such as OH, Br, I, OC(O)R, SR$_2$.

$$CH_3\text{-}LG + X^- = CH_3X + LG^- \qquad (22)$$

As the biochemical processes leading to specific organochlorine compounds are studied in detail, it is likely that more subtly differentiated variants of these basic reaction types will become evident and possibly even new classes of halogenating enzymes will be discovered. For instance, in a recent preliminary report by Gerwick *et al.*[299] of a study of the biosynthesis of the molluscicidal metabolite, barbamide **51**, the trichloromethyl group appears to arise specifically from the unactivated *pro-S* methyl group of a leucine precursor and not from the *pro-R*-methyl. A novel, as yet undefined, process of regiospecific polychlorination appears necessary to explain this[299,300] with the authors of the original report suggesting a radical mechanism. Of possible relevance may be the observation by Heinecke and others that hypochlorous acid generated by neutrophils may, in the presence of excess chloride ion, generate molecular chlorine [eqn. (23)].

$$HOCl + Cl^- + H^+ = Cl_2 + H_2O \tag{23}$$

Some of the chlorinated products associated with neutrophil action are consistent with molecular chlorine addition to a double bond. It is conceivable that molecular chlorine formed in a similar process may also effect radical processes with saturated C–H groups (with multiple chlorinations associated with known solvent cage effects) proposed by Gerwick *et al.*[299].

Neidleman and Geigert[652] have suggested that marine organisms purposefully synthesize chlorinated metabolites, investing energy in chlorination and chlorinating enzymes to achieve key transformations in their biosynthesis because of the usefulness of such products to the organism. (Halometabolites and their function have been discussed in Sections 3.4 and 4.3.) While most work has been devoted to the detection, isolation and characterisation of halometabolites released by organisms, much less is known about the biochemical routes by which such materials may be synthesised. Even less is known about the existence of halometabolites produced but not emitted by organisms. Harper, for example, has reported on the utilisation of chloromethane by species of fungi known not to emit such a compound, suggesting that chloromethane may have a metabolic role in species hitherto not suspected of emitting chlorinated compounds. In addition, mammalian halogenating enzymes, such as myeloperoxidase, are directly involved in defence against invading organisms, such as bacteria, fungi, and parasites and may also produce chlorinated metabolites, though whether as inadvertent by-products of defence or as purposefully produced materials playing particular roles is not yet known.

Kirk has reviewed in detail the mechanism of haloperoxidase catalysis[646] and the nature of individual haloperoxidases. The chemistry effected or mediated by chloroperoxidases (CPOs) is reminiscent of that of hypochlorous acid[653–659] with much mechanistic study and debate having focused on the nature of the intimate process and the degree to which the actual chlorinating species becomes free of its catalytic precursor.

In the absence of an organic substrate CPO catalyzes oxidation of chloride to molecular chlorine, though at a rate very much lower than the rate of enzymatic chlorination. This suggests that molecular chlorine is not a critical intermediate in such processes (and differences in substrate specificities confirm the view).[660] Wagenknecht and Woggon[659] suggest that chlorination catalyzed by CPO proceeds *via* Cl^+ transfer from a HOCl adduct to the substrate bound to the distal pocket of the enzyme. Libby *et al.*[656,661] believe that less than 2% of halogenation proceeds *via* free positive halogen, preferring a process involving direct chlorine transfer to a substrate bound to a CPO intermediate. They suggest that, with the kinetic data produced by Marquez and Dunford,[657] the assumption that hypochlorite is an obligatory intermediate in myeloperoxidase reactions should be questioned, the *N*-chloramine of taurine being a preferred reservoir for positive chlorine over HOCl and a much less discriminating an oxidant in neutrophils.[662]

Chlorinations involving CPO from *C. fumago* have been well studied. The first step involves reaction with hydrogen peroxide to give the hydroperoxide of the enzyme, so-called compound I. This reacts with chloride to give the enzyme intermediate, EOX. Discussion continues as to whether this is the actual chlorinating agent or whether it decomposes to give a Cl^+-carrier. The lack of substrate- and regio-specificity suggests that most substrates are chlorinated outside the active site.[658]

Much of the early work in the search for halogenating enzymes used monochlorodimedone **96** as substrate,[663] a compound that is not a natural substrate for such reactions. It is perhaps not surprising therefore that the types of haloperoxidases detected using this probe were all similar in having a protoporphyrin IX as the prosthetic group. However, bromoperoxidases isolated from bacteria were unable to effect chlorination to monochlorodimedone, suggesting other classes of haloperoxidases may exist. In bacteria,[664,665] **nonheme** haloperoxidases have been isolated that can effect catalyzed chlorination; for instance, that from *Pseudomonas pyrrocinia* is able to chlorinate monodechloroaminopyrrolnitrin **97** to aminopyrrolnitrin **98**.[666] These enzymes contain neither a co-factor (such as vanadium) nor prosthetic group (such as heme). Detailed studies on this type of enzyme reveal that a triad of amino acids, aspartic, histidine and serine, are necessary for halogenating activity,[667] a triad also associated with the hydrolysis of esters and amides. The first step in halogenation catalyzed by these enzymes is the formation of an acetate ester at the Ser residue, which is hydrolyzed by hydrogen peroxide to form peracetic acid which is the oxidizing species for halide, (information contained in a patent[668]) supported by recent structural[669] and mechanistic[670] studies. The authors suggest that a specific halide-binding site is absent from the enzymes but hydrophobic substrates may fit into the active-site pocket for selective halogenation, with the actual halogenation itself being uncatalyzed by these enzymes. Kirk and Conrad,[671] however, have suggested that the reported activity may be a common property of hydrolase enzymes, such as esterases and lipases.

The lack of substrate specificity suggests that these enzymes are unlikely to be involved in the biosynthesis of halometabolites which are the result of apparently regio- or stereospecific halogenation, such as pyrrolnitrin **99**, chloramphenicol **62** or barbamide **51**, a suggestion supported by other data.[672] The search for the enzyme which effects these regiospecific halogenations can only come from studies which involve natural substrates.[673] Chlorination of L-tryptophan **100** to 7-chlorotryptophan **101** is the first step in pyrrolnitrin biosynthesis by *Pseudomonas fluorescens* (chlorination using a haloperoxidase giving only the oxidised rather than the halogenated product). A second chlorination occurs later in the process, with monodechloroaminopyrrolnitrin **97** giving aminopyrrolnitrin **98**.[674,675] Both processes were found to require NADH, explained by the involvement of oxygen and the intermediacy of an epoxide, followed by halohydrin formation and dehydration. These processes have also been considered theoretically.[676] Halogenation catalyzed by perhydrolases and by the newly detected NADH/FAD-dependent halogenases has recently been reviewed.[677]

A different type of bromoperoxidase was isolated from the brown alga *Ascophyllum nodosum*[678] with a vanadium chloroperoxidase being characterised in 1995.[679] An X-ray structure was reported in 1996.[680] Another vanadium chloroperoxidase, isolated from the fungus, *Embellisia didymospora*, has been characterised and found to share 68% identity in its primary amino-acid structure with the enzyme isolated from *Curvularia inaequalis*, with conservation of all active-site residues.[681] These vanadium haloperoxidases are believed to effect unspecific electrophilic halogenations,[682,683] though recently Butler has reported that the nature of the oxidized halogen intermediate depends on the nature of the organic substrate. In the presence of indoles, vanadium bromoperoxidase does not release freely diffusible HOBr.[684]

The first halometabolite isolated from bacteria was the antibiotic chloramphenicol **62** produced by *Streptomyces ven-*

ezuelae.[685] Despite having been known since 1936, surprisingly little is known about its biosynthetic pathways. However, it is believed from studies of pathways leading to chloramphenicol and 7-chlorotetracycline, that the introduction of chlorine does not occur late in a biosynthetic process.[253] A series of intermediates formed in 7-chlorotetracycline **102** biosynthesis have been characterised, with the actual substrate for the chlorinating enzyme being 4-ketoanhydrotetracycline **103**,[686] though very little is known about the chlorinating enzyme which mediates this process.

Biogenic formation of monohalomethanes appears to proceed *via* a metabolic pathway not involving the haloperoxidases. Urhahn and Ballschmiter have reviewed three different pathways of biogenic formation of halomethanes.[453]

Wood-rotting fungi have long been known to produce chloromethane,[502,503] with, in the case of MeCl produced by *Phellinus pomaceus*, methionine suggested from isotope-labelling studies to be the source of the methyl group.[505] This has been confirmed by Harper and colleagues[402,406,407, 504] who proposed the direct incorporation of halide into a C1 compound probably catalyzed by a membrane-bound enzyme. Later work by Harper[404,405] indicated that chloromethane release and utilisation were widespread among wood-rotting fungi, with 61% of fungi studied from the genera *Phellinus* and *Inonotus* being able to biosynthesise chloromethane. Chloromethane acts as a methyl donor in the biosynthesis of veratryl alcohol, a secondary metabolite involved in lignin degradation in wood-rotting fungi. Watling and Harper,[410] in a recent review, provisionally estimate an annual source strength of 0.16×10^6 t from fungal emissions of chloromethane, 75% of which is released from tropical and sub-tropical forests. Wuosmaa and Hager have suggested[687] that an *S*-adenosyl-L-methionine (SAM) methyl transferase is responsible for halomethane biosynthesis both in wood-rotting fungi and in the marine red alga, *Endocladia muricata*. More recently, Ni and Hager[320,321] have isolated and investigated an enzyme from the common halophyte, *Batis maritima*, which catalyzes the formation of chloromethane from chloride and SAM. Harper found strong evidence that SAM was not an intermediate in the biosynthesis of chloromethane from L-methionine in the fungus *Phanerochaete chrysosporum*.[409] In a recent survey of 118 higher plants, Saini *et al*.[390] detected halide methyl transferase activity in 87 of these, with the highest activity in cabbages. The enzyme appears also to be involved in sulfur metabolism. The authors, noting that chloride sensitive species do not appear to have this activity, suggest that the activity may provide a mechanism for the elimination of halide ion and hydrosulfide, both of which are known to be phytotoxic to plants. More detailed studies on *Brassica oleracea*,[688] in which rate and inhibition parameters for a purified enzyme were obtained, suggest that the enzyme is more likely to be important for sulfur rather than halide metabolism.

In very recent studies on *Phellinus pomaceus*, Saxena *et al*. have demonstrated that the biosynthesis of MeCl is catalyzed by a membrane-bound *S*-adenosylmethionine, halide ion methyl transferase.[689] Manley[690] has also proposed that methylcobalamin may be linked with iodomethane formation in the marine environment. Interestingly, in a very recent study[222] Coulter and colleagues have isolated, from a soil-living micro-organism which uses chloromethane as the sole source of carbon, an enzyme which is able to effect rapid transfer of methyl from MeX, X = Cl, Br, I, to a series of anions including Cl^-, Br^- and SH^-. The enzyme contains cobalt in the form of cob(II)alamin, which may be reduced to cob(I)alamin prior to methylation to give methyl cob(III)alamin. Subsequent demethylation regenerated the Co^I state (see also ref. 691). Were the organism to be widespread in the environment, this very rapid transmethylation would have extremely important implications for estimates of the fluxes and burdens of the halomethanes, as well as wider environmental significance.

5.2 Biodechlorination

It has been known from the time of Paracelsus that, depending on the dose, exposure route and length of exposure, any compound (including those containing chlorine) will have physiological effects that may be beneficial, damaging or a combination of the two. In fact, the environmental recalcitrance of a compound may be the result of a toxic effect, preventing the growth of organisms capable of degrading them. This section explores this topic, referring briefly to progress being made in developing a fuller understanding of biodehalogenation from advances in biochemistry, physiology, genetics and molecular biology.

There has been a long-held belief that the carbon–chlorine bond is intrinsically environmentally recalcitrant, that is, organochlorines cannot be degraded in the environment. However, evidence that certain organobromine compounds (*e.g.* bromopropionate) can be used as the sole carbon and energy source by some bacteria has been known[692] for over 70 years. This recalcitrance has been associated with a presumed absence of metabolic routes associated with the xenobiotic nature of some of these materials.[693] However, not all chlorinated organics are recalcitrant: for instance, chloromethane, chloroethane, dichloromethane and 1,2-dichloroethane can serve as carbon sources to support growth.[222,694–697] A study of the mechanisms of dehalogenation is important, not least because it may provide an understanding of the evolutionary processes which have led to adaptation (including adaptation that weakens substrate specificity and which thereby broadens the substrates capable of being degraded).

The wealth of reliable and unambiguous evidence that chlororganics may arise through natural processes, are ubiquitous and are formed in large quantities focuses attention on the means by which such compounds containing carbon–chlorine bonds are broken down in the environment. Bearing in mind that production of organochlorine compounds is probably an ancient characteristic of the natural world, the concentrations now present require the existence of natural processes for effecting their breakdown and ultimate mineralization. Understanding of these processes will be relevant in the search for effective technologies to bring about the purposeful degradation of persistent man-made chlorinated pollutants and the purposeful remediation of contaminated media or their removal from waste streams (see for example refs. 698 and 699).

Degradability[700] will be related to the chemical characteristics of the organochlorine compound, its physical properties, particularly volatility and hydrophobicity, (discussed earlier in Section 3.4), where in the environment it is generated, how it is transported and migrates, where it accumulates, and the opportunities that thereby arise for its transformation chemically and biologically and ultimately its complete mineralisation to chloride ion, water and carbon dioxide. A full characterisation of the various chemical and metabolic pathways (and their rates and susceptibility to variations in factors such as temperature, pH and other important system variables) leading to complete mineralisation will be necessary, to assess the potential for the accumulation of intermediates more toxic than the materials being degraded or for incorporation of organochlorine residues into cellular biomass without complete mineralisation.

This section provides an illustrative survey of developments in the understanding of the processes of biological dechlorination and some of its implications and controversies. This is an extensive topic and is not reviewed comprehensively (see refs. 701–705).

First, it is now known that halogens may be cleaved enzymatically from haloalkanes, haloalkenes, haloaromatics, halogen-containing alcohols and acids and a variety of more complex chemical types by mono- and dioxygenases, halohydrolases, haloalkane halidohydrolases, dehydrohalogenases, halohydrin dehalogenases, haloacetate halidohyodrolases, glutathione transferases, laccases, tyrosinases, peroxidases, hydratases, and others. Microbiological dechlorination of poly- and perchlorinated compounds presents particular challenges arising from the hydrophobic character of many of these compounds. Reductive dehalogenations may be co-metabolic (that is, not coupled to energy conservation) or respiratory (involving the halocarbon as electron acceptor).[706,707] Isolation of pure cultures of bacteria demonstrating the latter type of behaviour has proved difficult. A bacterium has been isolated very recently[708–710] which can achieve the complete dechlorination of perchloroethylene and trichloroethylene to ethylene (requiring hydrogen as an electron donor). Significantly, other reducing co-factors (methanol, lactate, formate, pyruvate) support neither the growth of the organisms nor the dechlorination. Perchloroethylene and trichloroethylene are thus the electron acceptors in the process of anaerobic respiration. Genetic engineering is also providing modified organisms able, for example,[711] to effect degradation of pentachloroethane to glyoxylate and formate.

Enzymatic dehalogenations can be classified in a number of ways, including those involving reduction, oxidation, substitution and elimination.[701,703,704] A systematic classification of the enzymes responsible for such transformations has yet to appear, but one based on the mechanistic type of the transformation is currently believed[704] to be more useful than one based on substrate type:

reduction[712,713]: *e.g.* reductive dehalogenation in which C–Cl is replaced by C–H, eqn. (24):

$$CCl_2{=}CCl_2 + H^+ + 2\,e^- \;=\; CHCl{=}CCl_2 + Cl^- \qquad (24)$$

oxidation: *e.g.* oxidative dehalogenation in which C–Cl is replaced by C–OH, involving reaction with O_2, eqn. (25):

$$\begin{aligned}&1{,}2\text{-}C_6H_4Cl(CO_2H) + O_2 + NADH + H^+\\ &\quad = 1{,}2\text{-}C_6H_4(OH)_2 + NAD^+ + CO_2 + HCl \qquad (25)\end{aligned}$$

substitution: *e.g.* hydrolytic dehalogenation[714,715] in which C–Cl is replaced by C–OH on reaction involving H_2O, eqn. (26):

$$RCH_2Cl + H_2O \;=\; RCH_2OH + H^+ + Cl^- \qquad (26)$$

substitution: *e.g.* thiolytic dehalogenation in which $>CCl_2$ is converted to $>C{=}O$ *via* involvement of glutathione (GSH), eqns. (27)–(29):

$$CH_2Cl_2 + GSH \;=\; GSCH_2Cl + H^+ + Cl^- \qquad (27)$$

$$GSCH_2Cl + H_2O \;=\; GSCH_2OH + H^+ + Cl^- \qquad (28)$$

$$GSCH_2OH \;=\; GSH + H_2CO \qquad (29)$$

elimination: *e.g.* hydration by catalyzed addition of H_2O followed by chemical decomposition, eqns. (30)–(31):

$$HO_2CCH{=}CHCl + H_2O \;=\; HO_2CCH_2CH(OH)Cl \qquad (30)$$

$$\begin{aligned}&HO_2CCH_2CH(OH)Cl \;=\; HO_2CCH_2CH({=}O)\\ &\qquad\qquad + H^+ + Cl^- \qquad (31)\end{aligned}$$

elimination: *e.g.* dehydrohalogenation, eqn. (32):

$$c\text{-}C_6H_6Cl_6 \;=\; c\text{-}C_6H_5Cl_5 + H^+ + Cl^- \qquad (32)$$

substitution/elimination: *e.g.* intramolecular dehydrohalogenation, eqn. (33):

$$\begin{aligned}&HOCH_2CH(OH)CH_2Cl\\ &\qquad = HOCH_2\overline{CHCH_2O} + H^+ + Cl^- \qquad (33)\end{aligned}$$

transmethylation: *e.g.* enzyme-mediated[222,691] formation of chloromethane from bromomethane, eqn. (16):

$$MeBr\,(aq) + Cl^-\,(aq) \;=\; MeCl\,(aq) + Br^-\,(aq) \qquad (16)$$

Mention must be made of the exemplary studies of Janssen, Dijkstra, Verschueren and co-workers in the investigation of the intimate mechanism of dechlorination of 1,2-dichloroethane[716–724] which is contributing significantly to the understanding of biodegradation. The work also reveals some of the limitations of directed mutation in efforts to modify enzymic processes to make them more (or less) selective and more robust, for biotechnological applications. 1,2-Dichloroethane is a major industrial product believed to be entirely anthropogenic (though its formation by chloride-ion exchange from the naturally formed 1,2-dibromoethane cannot be entirely excluded (see Section 4.1)). The bacterium, *Xanthobacter autotrophicus* GJ10, can use 1,2-dichloroethane as the sole source of carbon, and from it a haloalkane dehalogenase capable of converting 1,2-dichloroethane to 2-chloroethanol has been isolated, purified and the gene encoding the enzyme sequenced. Crystallographic studies[716] show that substrate is converted to product *via* a two stage process. At pH 5 and 4 °C, the substrate sits in the active site; after the temperature has been raised to ambient, a C–Cl bond is broken, giving Cl^- (stabilized by hydrogen bonding to Trp125 and Trp175) and $–CH_2CH_2Cl$ bound at Asp124 (*i.e.*, aspartate at position 124 in the protein amino acid sequence for the enzyme). At pH 6, the ester group is hydrolysed by a water activated by His289-Asp260. Replacement of Asp260 in the catalytic triad by asparagine by site-directed mutagenesis results in a catalytically inactive mutant.[717] Debrominating activity of 1,2-dibromoethane could be restored to the latter by replacing Asn148 by aspartic or glutamic acid, though with a ten-fold reduction in the catalytic rate constant compared with the wild-type enzyme, caused by a 220-fold reduction in the rate of C–Br cleavage, a 10-fold reduction in rate of hydrolysis of the alkyl-enzyme intermediate. Br^- release was 12-fold faster though *via* a different pathway.

Interest has recently centred on how the processes and pathways for biodechlorination might have evolved and whether (and, if so, how) the organisms responsible may be genetically linked (‘phylogenetics’). In principle, this capability may be the result of recent adaptive pressure[693,719,725–730] associated with the release of anthropogenic chlorinated products into the environment (by processes analogous to the development of drug resistance in pathogenic bacteria) for which recent evidence from the microbiological degradation of 1,3-dichloropropene (presumed to be wholly anthropogenic) has been adduced.[731] Alternatively, the capability may have long existed as a consequence of the presence of chlorinated organics over biological time.[693,725] This has provided a further stimulation for the mapping the amino acid sequences of the active sites of enzymes performing identical functions but from different and geographically widely separated organisms.[732]

5.3 Chlorinated compounds in the human body

While inorganic chlorine, as chloride, is well known to be vital for human metabolism[49] being necessary for a range of physiological processes, such as digestion and renal function, the role of hypochlorous acid (and possibly molecular chlorine itself) in the functioning of our bodily defences is perhaps less well known. Hurst and Lymar[733] have recently reviewed the general topic of cellularly-produced inorganic oxidants.

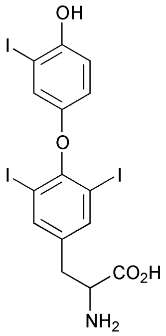
On the other hand, the presence of persistent organochlorines in the body, for example, from chlorinated pesticide residues, PCBs and PCDD/Fs, gives cause for concern because they may be bioconcentrated through various trophic levels in the food chain and, because of their lipophilic character, can be accumulated in the fatty reservoirs in the body. While the amounts are generally small and suggested long-term health effects difficult to ascribe unequivocally to their presence, the consequences of such long-term presence in the body requires better understanding. However, it is reassuring from a public and environmental health point of view that in most cases, the concentrations of these materials have been on a downward trend in the human body (as well as in the tissue of fish, birds and animals, and also in the environment generally) from the peak concentrations of the '60s and '70s. More volatile chlorinated products are not accumulated (though, of course, long-term continuous exposure may result in metabolite formation) and may be detected in exhaled breath.[734]

It is only quite recently that the possibility has been explored that the human body may itself be a producer of organochlorines. Showing whether or not organochlorines may be synthesised in the human body will be necessary properly to assess the risks associated with exposure to industrially produced organochlorines present in the environment (for their formation by metabolic processes would suggest that the body may have developed some tolerance towards them and some means of breaking them down). It has long been known (though not widely so) that organobromine compounds can be detected in the human body.

1-Methylheptyl-γ-bromoacetate **71**, isolated from human cerebrospinal fluid, is found to have anti-cholinesterase activity.[393,394] The further study of such compounds and of their physiological role is long overdue. The physiological role of the iodine-containing hormone, thyroxine **11**, has been extensively studied, with its metabolic effects in humans mediated *via* a 5′-deiodinated thyroxine **104**.[735]

Work recently summarised[736] has focussed on neutrophils, the white blood cells which combat invading infectious agents by the process of phagocytosis (and which are also associated with certain inflammatory diseases). Myeloperoxidase (MPO), a key enzyme in phagocytosis,[737] produces hydrogen peroxide, which in the presence of chloride ion, forms hypochlorous acid.[738–740] Zgliczyński *et al*. suggested in the 1970s[741,742] that HOCl from the MPO/H_2O_2/Cl^- system can form chloramines (and even dichloroamines, which may effect ring chlorination of tyrosine[743]) from amino acids. In 1982, Weiss and co-workers showed that neutrophils effected the formation of chloramines, such as *N*-chlorotaurine, from amino acids, such as taurine, and hypochlorous acid,[744] work extended recently by Winterbourn,[745] Heinecke[746] and others. Winterbourn and co-workers were also first to present evidence that these processes could lead to products containing carbon–chlorine bonds,[747] reporting the formation of two 9,10-chlorohydrins **105** and **106** from oleic acid and MPO, chloride and hydrogen peroxide. Arnhold *et al.* have published similar observations.[748] More recently, Heinecke[749] and Winterbourn[750] independently have shown that cholesterol chlorohydrins **107** and **108** could be formed. In *in vitro* studies which mimic physiological conditions, the formation of cholesterol dichloride **109**[751] and the direct detection of dichlorine[752] itself both suggest that elemental chlorine, Cl_2, may have a physiological role in the human body, associated with a well known[753] equilibrium [eqn. (23)].

Kettle, Winterbourn and co-workers have also shown that the tyrosine in human serum albumin exposed to MPO and stimulated neutrophils may be converted to 3-chlorotyrosine **110**.[754,755] Hazen and Heinecke have finally provided direct evidence[15] for chlorination in the human body by establishing that elevated levels of 3-chlorotyrosine may be found in low density lipoprotein isolated from human atherosclerotic lesions. Haas[756] has estimated the production of organochlorines in the body to be *ca*. 6–28 μg per day. Such estimates are bound to be crude. Further work is needed to refine such calculations, particularly in the light of a report[600] which raises the possibility, from mass balance studies of daily human dietary PCDD/F intake, that the human body is a net emitter of that group of most demonised of all organochlorines, the dioxins (PCDD/Fs: see Section 4.5). While such net emissions may simply be the result of the reduced burden of PCDD/Fs in the environment and hence in food, nevertheless, part of these emissions may be the result of *de novo* formation in the human body. Confirmation of the reported observations and investigation of the possible precursors for these materials is thus urgently needed.



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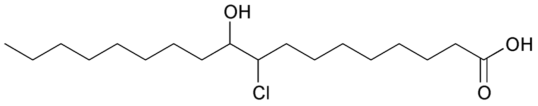

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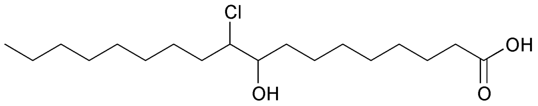

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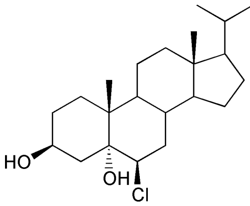

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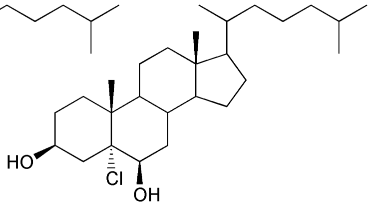

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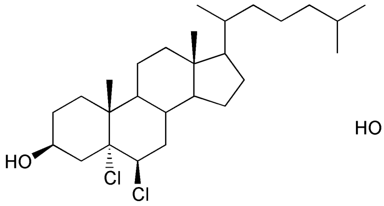

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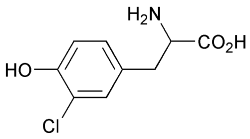

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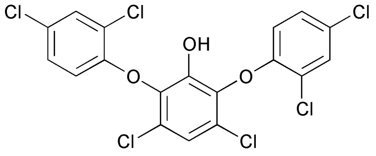

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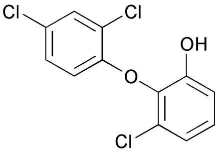


112

6. Distribution and physical transport

To assess the nature and degree of any risk associated with the presence in the environment of a particular component requires the availability of concentration data, their geographical variation and temporal trends (as well as the identification of routes to exposure and an understanding of the consequences of such exposure). The available data are often of limited value in assessing potential risk because they may have been collected from a single medium (sediment, river, atmosphere) at a small number of geographical locations over a limited period of time. Extrapolation to take account of geographical, compartmental, seasonal or other temporal variations requires the use of simplified models based upon a set of assumptions. Difficulty may arise when the output from modelling is used to drive regulatory activity without the uncertainties arising from the assumptions made being accepted or understood (see, for example, ref. 757 and earlier papers.) The study and development of models is thus a critical area of research. Confidence in the quality and relevance of model prediction requires the continuing collection of appropriate data, including data relating to the origins, natural and anthropogenic, of the materials of concern.

Any compound produced in or emitted to the environment (whether natural or man-made) will be transported and transformed as a consequence of its physicochemical properties, the physical, chemical, biochemical and biological characteristics of the environmental compartments and subcompartments (including the biota which inhabit them) in which such compounds are found and the time to which the compound is exposed to these conditions (see ref. 758 for a recent discussion of some of the relevant issues). An understanding, qualitatively and quantitatively, of these processes will be needed to establish the sources, sinks, reservoirs, fluxes and lifetimes (and hence impact on the environment) for materials involved in an elementary geochemical/geobiochemical cycle. A natural cycle involving emitted compounds, including those containing chlorine, would need to define (at least) a qualitative description of processes of transport and transformation, at the local, national, regional, continental and global levels (which will be governed by the characteristics of the source, which may be highly localised (a ‘point’ source, such as a chimney or from an individual plant) or diffuse (such as from an industrial site, a centre of human population, a forest, a country)). The earth, with its various geological compartments, media and associated ecosystems, can thus be seen as a chemical and biochemical reactor of considerable heterogeneity and complexity, varying dynamically with the periodicity of natural geochemical phenomena on various timescales. It is beyond the scope of this article to give other than a brief overview of this topic. Further information may be obtained from recent texts and reviews.[17,759–763]

Such understanding of the transport and fate of emitted compounds is predicated on the identification of the sources of these materials and their source strengths (see, for example, refs. 55–62). From this may be gauged the impact of man-made products on the environment (including the remote environment) which will include the identification (against the background of other potentially confounding natural processes) of those that represent serious risk to man and the environment,[764] the assessment of the need for control or remediation measures to be applied, judgements concerning control and remediation procedures that are likely to be most effective and cost-effective and the measurement of the effectiveness of such procedures.

Transport will take place in the hydrosphere (oceans, lakes, rivers, groundwater), in the atmosphere (troposphere, stratosphere, between the northern and southern hemispheres), the lithosphere and in the biosphere (*via* ingestion and excretion, migration, bioconcentration and bioaccumulation). There will be continual exchange between these various compartments as a result of volatilisation, dissolution and partitioning associated with deposition, precipitation, sedimentation and the lifecycles of biota.

Physical transport or mobility will be dependent on the physical properties of the material (see refs. 765 and 766 for recent studies on PCDD/Fs) and its propensity to suffer chemical change during the time spent subject to a particular set of conditions, physical (such as temperature, light flux) chemical (pH, presence of a putative reagent, such as water) or biological (presence of an organism capable of using the compound as a carbon or energy source). Intrinsic properties which will govern the tendency of a compound to migrate or be transported will include its molecular weight, chemical structure, vapour pressure, boiling and melting points, solubility in water, Henry’s constant, partition coefficient and optical characteristics (such as UV light cross-section). The tendency to migrate will also be governed by the characteristics and location of the medium in which the compound is found. If in air, its fate will be determined by its reactivity with aerial components, particularly initiators of oxidative degradation processes, such as hydroxide radicals (and possibly chlorine atoms: see Section 2.5) or the adsorption of photons of energy sufficient to effect photolytic breakdown with significant quantum yield. In addition, it may be partitioned between the air and other phases, such as gas–liquid exchange at the surface of water bodies, with the fluxes depending on the concentration in the liquid phase, Henry’s Law constant, temperature and wind speed. Similar processes are possible involving cloud or fog droplets or precipitation, such as rain or snow. Further chemical change, particularly hydrolysis, may follow such phase exchange. Hydrophobic material of low volatility may be preferentially adsorbed onto the surfaces of various atmospheric particulates, such as soot (primarily from biomass burning and from fossil fuel combustion), dust (ejected from volcanoes, from dust storms and soil erosion) as well as sea-salt aerosol and water droplets, or on to the surfaces of vegetation. Materials present as vapour in the atmosphere or as adsorbates hitching a ride on particulates suspended in the air will be subject to vertical and horizontal transport of short (local) medium (regional) and long (intercontinental, interhemispheric) range associated with processes of the circulation of air masses. They will be deposited or redeposited on land or water by processes of dry and wet deposition. Seasonal effects, such as precipitation as snow and the coverage of water bodies by ice, will occur.

In the aquatic environment, transport may occur as a consequence of processes of global ocean circulation, by bioaccumulation and bioconcentration in the various stages of the marine food chain, and by slow transfer into sediments on the ocean floor. Biosurfactants formed by marine organisms are known to accumulate at the ocean surface, producing a so-called ‘surface microlayer’ (see, for example, refs. 176 and 358), into which other marine organic products and pollutants may accumulate and be subsequently transported. Related processes in lakes, rivers and estuaries will occur in the freshwater aquatic environment. Precipitation and deposition of organic compounds onto soil (and their formation and transformation in the soil) may result in leaching of these materials into water percolating through the soil and accumulating as groundwater in underground reservoirs (‘aquifers’). Water-insoluble liquids with specific gravities greater than that of water, such as polychlorinated organic solvents, may percolate under gravity and accumulate in geological formations or in aquifers as separate phases. The lifetime of organic compounds in these media will be a function of intrinsic hydrolytic and oxidative stability and susceptibility to change, reductive and oxidative, as a result of biotic processes.

To be transported through the troposphere to enter the stratosphere in significant amounts, the atmospheric lifetime of an aerial component must be greater than about a year. Chloromethane fulfils this criterion and, consequently, insofar as its origins are natural, is seen as making a natural contribution to ozone depletion. The nature of global atmospheric circulation is such as to divide the atmosphere of the northern hemisphere from that of the southern by a so-called intertropical convergence zone, which effectively limits processes of exchange of air masses (and organic components contained therein) between the hemispheres. Because of the preponderance of industrial sources and population centres in the northern hemisphere, the relative concentrations in the two hemispheres of an atmospheric component with atmospheric decomposition rates less than the rate of interhemispheric exchange can be an indicator of a possible anthropogenic or natural source.[486]

In addition to such transport associated with global circulation, transport of so-called ‘semi-volatile’ materials may occur as a consequence of variations in mean temperature with season, altitude and latitude, resulting in a phenomenon variously known as cold condensation or global distillation (with transport occurring along a net negative temperature gradient) or global fractionation or chromatography (with air being the mobilising medium and the earth's surface, including soil and vegetation, being the stationary phase). Aspects of these phenomena have been discussed in more detail by Schreitmüller and Ballschmiter,[18] Simonich and Hites,[19] Wania and colleagues,[767–770] Cousins *et al.*,[771] Ockenden and Jones[760] and others.[772] Recently, Canadian workers[773] have established a 10- to 100-fold increase of the deposition of a series of semi-volatile organochlorine compounds between 770 and 3100 m altitude. For the less volatile materials the 10-fold increase is thought to be due to a 10-fold increase in snowfall over this change of altitude. However, a cold-condensation effect is thought to be responsible for the additional concentrations of more volatile compounds.

Simplified models are being developed to represent approximately the major factors which govern the global dispersion and distribution of persistent organic compounds, with compounds chosen for model development, testing and exemplification including hexachlorobenzene, 4-monochlorobiphenyl, γ-hexachlorocyclohexane and DDT,[768] PCDD/Fs,[774,775] PCBs,[775] and reactive volatile organic compounds, such as isoprene, α-pinene and methanol.[776] The global model developed by Wania and Mackay[768] represents the global environment in terms of six individual compartments (atmosphere, surface ocean, two soil compartments, fresh water, fresh-water sediment) in nine climatic zones (Northern and Southern tropic, N and S sub-tropic, N and S temperate, N and S polar and Northern boreal). Transport processes, diffusive or advective, can occur between the various compartments and the atmospheric and ocean compartments of adjacent zones.

Such models serve to highlight the absence of the physical and other data of the requisite accuracy that would be necessary for a reliable simulation of the global fate of a persistent organic compound. The need remains for continuing reliable and representative monitoring data on particular aspects of transport and distribution of especially long-lived chlorine-containing compounds, such as recently reported for PCBs,[757,777–780] γ-hexachlorocyclohexane,[772,780,781] C_1 and C_2 chlorohydrocarbons[782,783] and hexachlorobenzene.[780]

7. Anthropogenic or natural?

An acceptance of the proposition that organochlorine compounds found in the environment cannot automatically be assumed to be anthropogenic and that some anthropogenic pollutants may also have natural sources raises a critical question: is there a way to establish whether or not a chlorinated organic detected in the environment is present naturally or has been introduced as a pollutant? (Such a question may also focus on the origins of **any** organic environmental component of concern, including those not containing chlorine.) The answer becomes relevant when a chlorinated environmental component, assumed to be anthropogenic (or assumed to arise from an anthropogenic precursor) is associated with environmental damage or potentially unacceptable health effects. Such might be the case for chloroform (a water disinfection by-product), trichloroacetic acid (resulting from the atmospheric degradation of chlorinated solvents), chlorinated phenols, and even polychlorinated dibenzodioxins and dibenzofurans. However, these compounds are now known to have well established and widespread natural sources: for example, chloroform, trichloroacetic acids and chlorinated phenols are produced in natural processes in the soil. The point may be further illustrated by consideration of the diphenyl ether, Ambigol B, 2,6-bis(2,4-dichlorophenoxy)-3,5-dichlorophenol **111**, isolated as a secondary metabolite from a strain of the terrestrial blue-green alga, *Fischerella ambigua*.[784] It has marked anti-bacterial activity, just like the structurally very similar synthetic material, 3-chloro-2-(2,4-dichlorophenoxy)phenol **112** claimed by Colgate-Palmolive in a US patent, published at about the same time, for use in packaged anti-plaque oral formulations.[785]

How might it be possible unequivocally to distinguish between a sample of chloroform from a natural source and one produced synthetically? One approach that has been used extensively in geochemistry is stable isotope analysis,[86,87] particularly of $^{14/13/12}$C, $^{15/14}$N, $^{18/16}$O, $^{34/32}$S and $^{37/35}$Cl. These techniques are increasingly being used to study geobiochemical and other environmental processes,[786] particularly to characterise sources and associated physical and chemical phenomena. For example, carbon isotopic analysis has been used to differentiate sources of inorganic[787,788] and organic carbon, such as methane[789–791] formic and acetic acids[792] and VOCs.[793] Environmental processes have been probed using both δ^{13}C ($= 10^3 \times (^{13}C/^{12}C_{sample} - {}^{13}C/^{12}C_{standard}/{}^{13}C/^{12}C_{standard})$) and Δ^{14}C to characterise the materials present in ground water,[794] to study physical[795] and biochemical[796] processes in the sea and to monitor *in situ* biodegradation of hydrocarbons and chlorinated solvents.[797–799] Carbon isotope compositions for chloromethane are reported[800] to be different for samples from urban and marine atmospheres, though the origins of this effect are unclear. In principle, the use of Δ^{14}C should enable the required distinction to be made, since anthropogenic products derived from fossil sources will have negligible ^{14}C content whereas those from natural sources are expected to be equilibrated with atmospheric carbon-containing proportions of ^{14}C resulting from both natural γ-ray bombardment and from the atmospheric nuclear explosions of the 1950s and 1960s. However, the quantities of material required for reliable analysis have not yet allowed the measurement of Δ^{14}C for organochlorines isolated from the environment, even for the most abundant material, chloromethane.[801] On the other hand, δ^{13}C has been measured for chloromethane, present in the atmosphere at ppt levels.[802] It has recently been suggested[803] from δ^{13}C measurements that industrially produced MeBr maybe isotopically distinct. Large carbon-isotope fractionation has recently been observed from both bacterial oxidation[804] and abiotic transformation[805] of chloromethane and bromomethane, highlighting the importance of identifying the critical processes in environmental transformation and transport and the measurement of associated isotope fractionation. Furthermore, as the halogen is found to be labile in some of the transformations of these compounds,[222,806] δ^{37}Cl approaches (see below) may not be applicable.

Stable chlorine isotope analysis[807] of inorganic chloride has been used to study the origin of brines,[808] salt deposits and pore water from sediments.[809] Its use in the study of environmental processes has until recently been limited because of the small range of the parameter used, δ^{37}Cl ($= 10^3 \times (^{37}Cl/^{35}Cl_{sample} - {}^{37}Cl/^{35}Cl_{seawater}/{}^{37}Cl/^{35}Cl_{seawater})$), with most variation being within 1.0 ‰ (per mil) of ocean water chlorine. However, a very recent report[810] describes changes in δ^{37}Cl for chloride ion and for trichloroethylene in groundwater from a contaminated site. These observations suggest that natural attenuation processes are at work. However, it has also been shown that chlorine isotope fractionation can be affected by temperature and pressure, with fractionation occurring during organochlorine synthesis (and presumably, breakdown). The interpretation of data from isotope measurements thus requires a degree of caution until more of the physical, chemical and biochemical effects are better understood. Nevertheless, the possibility that anthropogenic chlorinated compounds might have a distinctive isotopic signature or 'fingerprint', has led to the suggestion that such fingerprints might enable the sources of pollution events to be identified. As a first step, van Warmerdam and colleagues[811] have used stable isotope measurements for carbon and chlorine to fingerprint the chlorinated solvents, perchloroethylene, trichloroethylene and 1,1,1-trichloroethane, from four manufacturers, finding $\delta^{37}Cl$ to vary between −3.5 and +6.0‰ and $\delta^{13}C$ between −37.2 and −23.3‰. It should be noted that these were bulk unused products and not used materials isolated from the environment. Samples isolated from the environment are likely to have been subjected to a range of physical, chemical and biochemical fractionation processes that may confound clear conclusions. The methodology used has been criticised[812] and further developed[813] to provide data on both carbon and chlorine isotopes from a single 1–2 μL sample of chlorinated solvent. It is thus likely that this technique will develop and be applied, though whether it will have the reliability and resolution to identify a pollutant as arising from a particular supplier (when taking into account such issues as variations in raw materials, processing conditions, swap and purchase-for-resale deals) remains to be seen.

More recently, variations in ^{37}Cl content of size segregated sea-salt aerosol (material produced by the action of wind and wave at the ocean surface (see Section 2.3)) from the marine boundary layer, as measured by $\delta^{37}Cl$, are believed to be consistent with processes of acid displacement of HCl[814] for mid-size aerosols and chlorine loss by a different mechanism for larger size aerosols,[815] possibly release of so-called 'reactive' forms of chlorine, such as HOCl, Cl_2, ClBr or $ClNO_2$.

8. Future research

The foregoing brings together the results of work from a variety of sources and disciplines, much of it done in isolation. There is now sufficient evidence for the role of chlorine in a range of natural processes to suggest the need to study explicitly natural cycles involving chlorine and to approach this from a range of inter- and multidisciplinary perspectives.

Many different lines of research will present themselves to individual analytical chemists, geochemists, biologists, atmospheric and marine scientists, human physiologists, ecologists and environmental scientists. Some of these topics will already be active on-going areas or work and will have provided the basis of this survey. What is needed is a wider dissemination of the results, and an assessment of their implications leading to the identification and prioritisation of the outstanding challenges that remain.

My personal selection of research targets, governed by major areas of uncertaintly and relevance to providing the basis of a natural chlorine cycle, would include:

- An improved mass balance for chloride inputs to and outputs from the oceans.
- Further studies of the terrestrial geochemistry and biogeochemistry of chloride ion.
- Further investigations of the heterogeneous atmospheric chemistry of chlorine, particularly the formation of positive or reactive inorganic chlorine species and its consequences.
- Better estimates of atmospheric atomic chlorine concentrations and their temporal and spatial variation.
- Detection of 'sentinel' compounds for reaction with chlorine atoms (such as **10**) in the atmosphere.
- Better understanding of the role of chloride ion in photosynthesis.
- Better understanding of the role of chlorine in the human body, with better estimates of the amounts of chloroorganics (and bromoorganics) formed *de novo* in the body and the role and fate of *de novo* generated chlorinated organics.
- The further use of natural abundance isotope ratio techniques to examine the possible origins of chlorinated organics isolated from the environment.
- Measurement of long-term historical trends of chloromethane concentrations in the atmosphere from the study of ice cores.
- Further studies on the physiological and biochemical function of organochlorines and the metabolic pathways for their production in the organisms know known to emit, produce or utilise them.
- The development of new techniques for the characterisation of soil AOX and for the study of the biogeochemistry of soil chloride and mobilisation and sequestration of organchlorines in soil and sediments.
- Further study of the identity, origin and concentrations of organochlorines in precipitation.
- Examination of the fate of PCDD/Fs in the body and establishment of whether or not the body produces them.
- Further examination of the chemical and biochemical mechanisms of biochlorination.
- Studies of the paleogenetics of microbial chlorination and dechlorination to establish its recent or historic origin.
- Development of environmental models with the on-going collection of environmental monitoring data to test their validity.

It is encouraging that over 75% of the papers cited have appeared since 1990 (55% since 1995), suggesting that, amongst some researchers at least, the view that organochlorine compounds are somehow 'unnatural' is no longer accepted and the natural chemistry of chlorine is a topic worthy of more detailed investigation. It is hoped that this review may both stimulate a wider appreciation of this conclusion as well as the study of these and other topics concerned with natural processes involving chlorine.

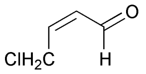
9. Endpiece

The wealth of information and knowledge brought together from widely dispersed sources, taken together, should provide convincing evidence for the existence of a range of geological, chemical and biochemical cycles involving chlorine in both inorganic and organic forms and provide a basis for further work to explore, define and understand their key components. In widening an appreciation of the natural world, and the impact that mankind is having on it, it is to be hoped that the benefits associated with the use of all synthetic chemicals, including those of chlorine, can be maximised and the (inevitable) deleterious consequences of their production, use and disposal can be minimized to provide for a more sustainable long-term future. More immediately, whether or not we can bring quickly wider access to safe drinking water to millions of people who currently do not have it (25 000 of whom die every day because this is so) or provide countries where malaria is a killer disease with DDT as the most effective means currently available to control the mosquito that transmits it, depends on a rational and objective assessment of all the evidence for and against the various possible options. I hope this review may play a small part in allowing this to happen.

10. Addendum

Since the submission of the manuscript a number of relevant and important publications have appeared. These are noted briefly below according to the section of the review to which they are most relevant. They serve to highlight the on-going interest in the topics surveyed and the need constantly to take account of new work in forming judgements on complex and critical matters.

1. Two general texts have appeared. The first reviews the technological and industrial signficance of chlorine and its compounds;[816] the second sets out the arguments for a phase-out of the chlorine industry and proposes a new approach to pollution prevention.[817] Ref. 817 includes a section on proposed natural sources of organochlorine compounds that, unfortunately, does not take account of the wealth of recent (post-1997) work which has been brought together in this review. The author challenges some of the evidence for the natural formation of organochlorine compounds and argues for the irrelevance of much of the rest. **2.1** A third text describes the evolution and economic importance of evaporites.[818] **2.2** Laboratory studies of hydrothermal processes occurring at high temperatures and pressures (such as occur in geothermal vents at the sea floor) have been reviewed,[819] including the decarboxylation of halogen-containing carboxylic acids in the temperature range 383–533 K. **2.4** Atmospheric vertical profile measurements[820] (below 21 km) of HCl as a proportion of total inorganic chlorine (HCl/Cl_y) reveal a 31 ± 9% increase from 1993 to 1997 following the Mount Pinatubo eruption. **2.5** Finlayson-Pitts and co-workers report[821] that the distribution of ions in an aqueous aerosol particle, such as sea-salt aerosol, is not uniform. Chloride ions appear to concentrate at the air–water interface, an observation that has implications for the production of volatile halogen-containing compounds from sea-salt aerosol and current attempts to model such processes. The stoichiometry (see eqn. (3)) of the reaction between Cl^- and mixtures of aqueous nitric and sulfuric acids and associated second-order kinetics have been confirmed.[822] Dibromine is formed[823] during heterogeneous interactions of Cl_2, HCl and BrCl with the surfaces of bromide-containing ice. 4-Chlorocrotonaldehyde **113** has been proposed[824] as a further 'sentinel' compound for the role of chlorine atoms in tropospheric chemistry. 28 ± 8% **113** is formed as the sole chlorine-containing organic product from the reaction of Cl with 1,3-butadiene **114** (emitted from motor vehicles) at room temperature in air. The proportions of HCl (from H abstraction) and C_5H_8Cl (from Cl addition) have been measured in studies[825] of the reaction of isoprene with chlorine atoms. The branching ratio for HCl formation is 17.4 ± 4%. Two modelling studies have appeared, one concerned with halogen chemistry in the Arctic boundary layer during polar sunrise,[826] the other with the atmospheric chemistry of iodine in the marine boundary layer.[827] **3.2** Unusual and complex chlorine-containing compounds, such as **115**, continue to be isolated[828] from natural sources (with appropriate control studies establishing their non-artefactual origin). The isolation of herbacic acid **116**, a trichloroleucine metabolite similar to **39**, has been reported.[829] **3.3.2** Harper has reviewed recent developments in the study of the global chloromethane cycle,[830] particularly those which indicate that the greater part of annual chloromethane flux arises not from the oceans but from terrestrial sources. Khalil and Rasmussen show[831] that soils (representative of a series of ecosystems) are net emitters of chloroform and net sinks for chloromethane. The latter observation magnifies the discrepancy between known sources of chloromethane and global flux estimates based on measured tropospheric concentrations and losses *via* reaction with hydroxyl radical, $HO^•$. Global burdens and distribution of $HO^•$ have been updated.[832–834] Errors which might arise from experimental methods used to study surface–atmosphere trace gas exchange have been evaluated.[835] Lee-Taylor and Holland have estimated[836] that soil litter decomposition may give rise to annual fluxes of $(0.5 - 5.2) \times 10^3$ t per year of bromomethane. Less bromomethane than previous estimated is emitted from vehicles powered by lead-containing gasoline.[837] A series of short papers has presented updates on bromomethane fluxes, sources and sinks.[838–840] **3.4** The potential for the development of non-opioid analgesics has been reviewed briefly,[841] following the isolation of epibatidine **40** from frog skin. The synthesis of geodin **17** is under study[842] as **17** is the spirocoumaranone subunit of **117** a candidate for treating certain feeding disorders. **4.2** Data on the concentrations and fluxes of chloroacetic acids in rain and natural waters in Switzerland have appeared.[843] **4.5** Further discussion has appeared of the global distribution of PCDD/Fs,[844] the distribution of PCDD/Fs in the atmosphere, soil, sediment and water,[845] time trends in local PCDD/F deposition,[846] the importance of combustion[847–849] as sources of PCDD/Fs and of processes which might lead to PCDD/F formation in incineration.[850–852] Measured and estimated partitioning between air and particles of PCDD/Fs has been examined as a function of chlorine content.[853] Rats fed nonachloro-2-phenoxyphenol convert it to OCDD.[854] **5.1** Van Peé and Ligon have reviewed[855] the bacterial biosynthesis of pyrrolnitrin **99** and other phenylpyrrole derivatives. A novel halogenase which chlorinates tryptophan **100** to 7-chlorotryptophan **101** has been isolated.[856] **5.2** Recent studies[857] conclude that 29–37% of the annual losses of hexachlorocyclohexanes (HCHs) from the Arctic Ocean arise from microbial degradation. Rapid anaerobic degradation of toxaphene has been observed in sewage sludge.[858] Poeleraends *et al*. have concluded[859] that a series of gram positive haloalkane-utilizing bacteria isolated from geographically widely separated sites have recently arisen from a common ancestor. **5.3** Vitamin C (at physiological levels) is reported to protect low-density lipoprotein against hypochlorous acid-induced oxidative damage.[860] Molecular chlorine generated by the myeloperoxide–hydrogen peroxide–chloride system (*in vitro*) effects chlorination of cytosine in bacterial RNA to give **118**.[861] 8-Chloroadenine **119** has also been identified in independent related studies.[862] Further studies of protein modification by hypochlorous acid[863–866] and related bromine-containing oxidants[867,868] have been reported. **6.** A recent reinvestigation[869] of the decline in concentrations of the components of toxaphene (a complex mixture of hexa- to decachlorinated bornanes and bornenes) in Lake Superior and Lake Ontario suggests that the rates of decrease are slower in large and cold lakes compared



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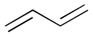

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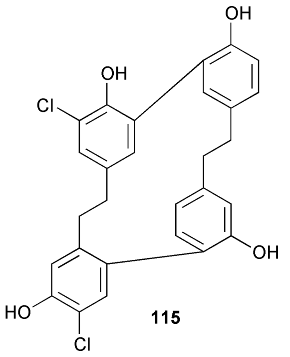

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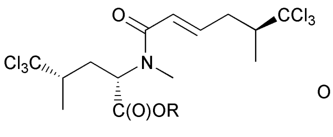

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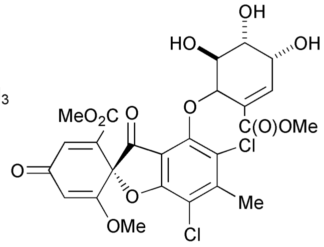

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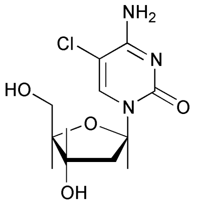

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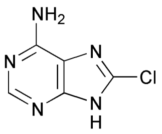

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with relatively small and warm lakes. The temporal trends in the decline of persistent pollutants such as polychlorinated biphenyls in biological material such as herring gull eggs may not simply be indicative of overall decline in the wider environment but can be affected by alterations in diet arising from changes in the structure of the food-web.[870] A new global multimedia model seeks to simulate transport, partitioning and degradation of persistent organic pollutants, such as HCH.[871] Cortes and Hites[872] have discussed some of the sampling and analytical requirements that are necessary to permit statistically significant temporal trends in atmospheric concentrations of semi-volatile compounds to be observed. **7.** More work has appeared on the fractionation of ^{12}C and ^{13}C in the biodegradation of trichloroethene and related compounds.[873] Compound specific ^{12}C : ^{13}C ratios for chloromethanes and chloroethanes have been determined for aqueous samples.[874] **9.** The issues posed by DDT house spraying for the eradication of re-emerging malaria have been discussed.[875,876]

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Clean solvent-free dipolar cycloaddition reactions assisted by focused microwave irradiations for the synthesis of new ethyl 4-cyano-2-oxazoline-4-carboxylates

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1,3-Dipolar cycloaddition reactions without solvent under focused microwave irradiation are reported. Imidate **3**, derived from ethyl α-cyano α-amino acetate as potential azomethine ylide, undergoes highly regioselective cycloadditions to a wide range of aldehydes **4a–f** as dipolarophiles in short reaction times. This simple, efficient and environmentally-friendly methodology has been applied to the synthesis of new ethyl 4-cyano-2-oxazoline-4-carboxylates **6a–f** in good yields (81–98%) and moderate diastereoisomeric ratios.

Introduction

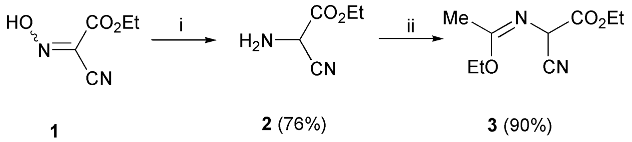
Concerns for the environment are increasing pressure to reduce the amounts of pollutants,[1] including organic solvents and the more drastic restrictions on 'solvent pollution' will require the adoption of solvent-less reaction conditions.[2] With the development of microwave ovens,[3] solvent-less reactions have become easier due to their high efficiency and convenient work-up conditions.

Our interest in this field has been focused on the synthetic use of imidates[4] derived from α-amino esters and aldehydes in 1,3-dipolar cycloadditions. In previous work we have described the use of imidates derived respectively from methyl glycinate[5] and dimethyl aminomalonate[6] in 1,3-dipolar cycloaddition reactions using solvent free-conditions.

According to the versatility associated with 2-oxazoline[7] moieties as synthetic precursors[8] in medicinal chemistry[9] and as protecting groups[10] in a wide variety of chemical syntheses, we report on the new eco-friendly synthesis of ethyl 4-cyano-2-methyl-2-oxazoline-4-carboxylates with imidate **3** derived from ethyl α-amino α-cyano acetate. Most of the reactions described herein are performed in open glass containers using neat reactants under solvent-free conditions in a focused MW oven[11] operating at 2450 MHz. In all cases, the comparisons of the MW-accelerated reactions have been made by conducting the same reaction in an oil bath previously heated at the same bulk temperature.

Results and discussion

As outlined in Scheme 1, the imidate **3** was easily obtained on a large scale according to a two step procedure. In the first step, ethyl cyano(hydroxyimino)acetate[12] **1** was reduced to the corresponding ethyl α-amino α-cyano acetate[13] **2** by sodium dithionite[14] in neutral aqueous solution and extracted with ethyl acetate. The dried extract was evaporated and gave **2** as a viscous oil in 76% yield. Next, treatment of **2** with triethyl orthoacetate in anhydrous methylene chloride under nitrogen at 41 °C provided the expected imidate[15] **3** after purification by distillation under reduced pressure in good yield (90%).



Scheme 1 Preparation of ethyl 2-cyano-2-(1-ethoxyethylidene)aminoethanoate **3**. *Reagents and conditions*: i, $Na_2S_2O_4$ 3 equiv., sat. $NaHCO_3$ 35 °C, 35 min then 4 h at 25 °C; ii, $MeC(OEt)_3$, CH_2Cl_2, Δ, 48 h.

The synthesis of ethyl 4-cyano-2-methyl-2-oxazoline-4-carboxylates **6a–f** (Scheme 2) was readily achieved according to the following solvent-free procedure: a mixture of freshly distilled aromatic aldehyde **4** and imidate **3** was heated at 70 °C without solvent in an oil bath with vigorous stirring. This reaction was monitored by ^{1}H NMR spectroscopy: the analysis of the crude reaction mixture indicated the formation of the expected cycloadduct **6** as a mixture of diastereoisomers (**6** *trans* and **6** *cis*) together with ethanol. After elimination of alcohol *in vacuo*, the mixture of diastereoisomers **6** was isolated in good yields (Table 1) and purified by chromatography on silica gel 60F 254 (Merck). In some cases, the diastereoisomeric enrichment of the diastereoisomeric mixture was realized by simple precipitation in the appropriate solvent, the pure diastereoisomers **6e** *trans* and **6f** *cis* were insoluble in ether and methylene chloride, respectively.

When the reaction was conducted at 70 °C in a focused microwave oven, several experiments were performed, at various powers and irradiation times, in order to find the most adequate conditions. Extraction of the reaction mixture from the microwave reactor with methylene chloride, elimination of

Green Context

Oxazolines are versatile synthetic precursors with applications in medicinal chemistry, as a protecting group and in a variety of chemical syntheses. Unfortunately their synthesis traditionally involves the use of substantial volumes of solvent and the production of large amounts of waste. Here a low-waste method is described for the synthesis of one important example of an oxazoline. The method is based on the use of focused microwave irradiation and the total avoidance of solvent. Product yields compare very well to those obtained using conventional methods. ***JHC***

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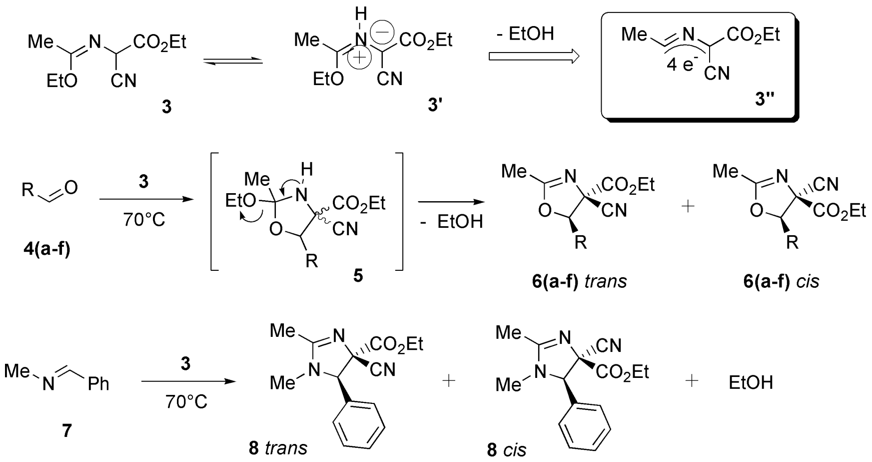
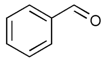
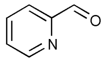
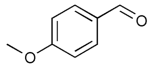
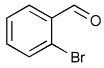
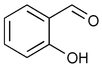
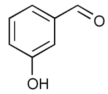
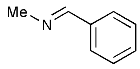


Scheme 2 Solvent-free dipolar cycloaddition reactions with imidate **3**.

Table 1 Results of solvent-free dipolar cycloaddition reactions of imidate **3** with aldehydes **4a**–**f** and *N*-benzylidene methylenamine **7** at 70 °C in an oil bath and under focused microwave irradiation

			Yield of cycloadduct[a] (%)			Reaction time/h	
Dipolarophile		Cycloadduct	Oil bath[b]	MWI[c]	*trans* : *cis*[d]	Oil bath	MWI
	**4a**	**6a**	92	93	87 : 13	1	1
	**4b**	**6b**	93	98	60 : 40	2	1
	**4c**	**6c**	86	87	63 : 37	6	4.5
	**4d**	**6d**	96	97	63 : 37	2	1
	**4e**	**6e**	92	90	83[e] : 17	2	1
	**4f**	**6f**	95	94	72 : 28[f]	1	1
	**7**	**8**	97	91	85 : 15	3	1

[a] Yield of isolated product. [b] Reactions were run in a thermostated oil bath, variation ±1 °C. [c] MWI = Microwave Irradiation by focused oven (Synthewave® 402, Prolabo). [d] Calculated from ^{1}H NMR spectra of the crude reaction mixture ($CDCl_3$, Bruker AC 300P, TMS as internal reference). [e] **6e** *trans* is separated by recrystallization in Et_2O. [f] **6f** *cis* in methylene chloride.

solvent followed by the analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated the formation of the cycloadducts **6** with the same diastereoisomeric ratio and with shorter reaction times (Table 1).

For all the syntheses, the formation of a single regioisomer **6** is in agreement with a highly regioselective 1,3-dipolar cycloaddition but the primary cycloadducts **5a–f** could not be isolated (Scheme 2).

The diastereoisomeric ratio and the structural assignment of these cycloadducts **6a–f** are based on spectroscopic data (^{1}H and ^{13}C NMR, mass spectrometry). For example, **6e** (R = 2′-hydroxyphenyl) exhibits two quadruplets for the ethyl ester groups (C-4), one at high field (**6e** *cis*, δ 1.22) indicating a *cis* relationship[16] with respect to the phenyl group on C-5 and the other at δ 1.32 (**6e** *trans*); the H-5 protons appears respectively at δ 6.23 (**6e** *trans*) and at δ 6.32 (**6e** *cis*). The diastereoisomeric composition of the crude product **6e** was determined by integration of these signals.

As shown by the results in Table 1, the use of focused microwave irradiations without solvent gave high yields under very mild conditions in a short reaction time (Table 1) with the same moderate diastereoisomeric composition. The simplicity of the experimental procedures renders this method particularly attractive. Soft reactions of imidate **3** activated by two electron withdrawing groups and aromatic aldehydes **5a**–**f** as dipolarophiles open a simple route to a wide range of novel ethyl 4-cyano-2-methyl-2-oxazoline-4-carboxylates **6a**–**f**. In these cycloadditions, immidate **3** is in equilibrium with azomethine ylide **3′** by thermal 1,2-prototropy[17] which is regarded as the synthetic equivalent of nitrile ylide **3″** after elimination of ethanol (Scheme 2).

In a similar way, we have also studied the addition of imidate **3** to the commercially available *N*-benzylidene methylamine **7** as dipolarophile (Scheme 2). The same reactions conditions (without solvent at 70 °C in an oil bath or under focused microwave irradiations) were applied to **7**, and gave the desired ethyl 4-cyano-2-methyl-5-phenyl-2-imidazoline-4-carboxylate **8** in good yields (Table 1). ^{1}H NMR analysis of the crude reaction mixture showed the formation of the cycloadducts **8** as a mixture of diastereoisomers (*trans/cis*: 85/15) together with ethanol before purification by flash chromatography on silica gel.

Experimental

Standard procedure using a focused microwave oven

A mixture of ethyl 2-cyano-2-(1-ethoxyethylidene)aminoethanoate **3** (1 g, 5 mmol) and freshly distilled aromatic aldehyde **4** (5 mmol) was placed in a cylindrical quartz tube (Ø = 4 cm). The tube was then introduced into a Synthewave® 402 Prolabo microwave reactor [2.45 GHz, adjusted power within the range 0–300 W and a wave guide (single mode T_{01}) fitted with a stirring device and an IR temperature detector]. Microwave irradiation was carried out at 70 °C for the appropriate reaction time (the microwave oven is monitored by a computer which allows the temperature of the reaction mixture to be adjusted). The mixture was allowed to cool down. After addition of methylene chloride (15 mL) in the reactor and removal of solvent *in vacuo*, the crude residue was purified by chromatography on silica gel (60F 254, Merck) with the appropriate eluent. Solvent evaporation gave the desired compound **6** as a viscous oil which crystallized on standing and was characterized by ^{1}H, ^{13}C NMR and HRMS analysis.

Ethyl 4-cyano-2-methyl-5-(pyridin-2′-yl)-2-oxazoline-4-carboxylate (6b)

HRMS, *m/z*: M$^+$ 259.0938 (calculated for $C_{13}H_{13}N_3O_3$: 259.0953). R_f = 0.64 with AcOEt/CH_2Cl_2 (1 : 1) as eluent. **6b** *trans*. ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) 1.39 (t, 3 H, *J* = 7.1 Hz), 2.25 (s, 3 H), 4.42 (q, 2 H, *J* = 7.1 Hz), 6.13 (s, 1 H), 7.27–8.68 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) 13.90 (qt, *J* = 128, 2.8 Hz), 14.09 (q, *J* = 131 Hz), 64.37 (tq, *J* = 149, 4.3 Hz), 76.72 (s, C-4), 86.16 (d, *J* = 161 Hz, C-5), 114.02 (d, *J* = 6.7 Hz, CN), 120.39 (ddd, *J* = 164, 7.2, 2.2 Hz, C-5′), 124.24 (dt, *J* = 165, 7.3 Hz, C-3′), 137.31 (dd, *J* = 163, 6.3 Hz, C-4′), 149.96 (ddd, *J* = 180, 7.1, 3.5 Hz, C-6′), 154.15 (m, C-2′), 165.60 (q, *J* = 2.6 Hz, C-2), 171.18 (qd, *J* = 6.9, 1.8 Hz, CO). **6b** *cis*. ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal ref.) 0.94 (t, 3 H, *J* = 7.1 Hz), 2.27 (s, 3 H), 3.86 (m, 2 H), 6.05 (s, 1 H), 7.27–8.68 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) 13.48 (qt, *J* = 128, 2.5 Hz), 14.17 (q, *J* = 131 Hz), 63.23 (tq, *J* = 149, 4.6 Hz), 75.22 (d, *J* = 2 Hz, C-4), 87.88 (d, *J* = 159 Hz, C-5), 117.04 (d, *J* = 6.6 Hz, CN), 120.94 (ddd, *J* = 163, 6.7, 2.2 Hz, C-5′), 123.94 (dt, *J* = 165, 7.5 Hz, C-3′), 136.99 (dd, *J* = 163, 6.2 Hz, C-4′), 149.43 (ddd, *J* = 180, 6.9, 3.5 Hz, C-6′), 153.75 (m, C-2′), 163.72 (m, C-2), 171.44 (qd, *J* = 7.2, 1.7 Hz, CO).

Ethyl 4-cyano-5-(2′-hydroxyphenyl)-2-methyl-2-oxazoline-4-carboxylate (6e)

HRMS, *m/z*: M$^+$ 274.0971 (calculated for $C_{14}H_{14}N_2O_4$: 274.0953). **6e** *trans* (R_f = 0.62 with AcOEt as eluent). Mp = 68–70 °C from Et_2O. ^{1}H NMR (200 MHz, $CDCl_3$, TMS as internal ref.) 1.32 (t, 3 H, *J* = 7.1 Hz), 2.22 (s, 3 H), 4.35 (q, 2 H, *J* = 7.1 Hz), 6.23 (s, 1 H), 6.77–7.33 (m, 5 H, Ar), 8.64 (brs, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS as internal ref.) 13.90 (qt, *J* = 128, 2.5 Hz), 14.05 (q, *J* = 131 Hz), 64.22 (tq, *J* = 149, 4.7 Hz), 76.92 (s, C-4), 84.19 (dd, *J* = 161, 2.6 Hz, C-5), 114.46 (d, *J* = 8.1 Hz, CN), 115.32 (dd, *J* = 169, 7.6 Hz, C-3′), 120.43 (dd, *J* = 163, 7.9 Hz, C-5′), 121.44 (d, *J* = 7.2 Hz, C-1′), 125.61 (dm, *J* = 160 Hz, C-4′), 130.51 (dd, *J* = 161, 8.8 Hz, C-6′), 153.13 (m, C-2′), 166.44 (m, C-2), 171.83 (q, *J* = 7.3 Hz, CO). **6e** *cis* (R_f = 0.72 with AcOEt as eluent). ^{1}H NMR (200 MHz, $CDCl_3$, TMS as internal ref.) 1.22 (t, 3 H, *J* = 7.2 Hz), 2.27 (s, 3 H), 4.09 (q, 2 H, *J* = 7.2 Hz), 6.32 (s, 1 H), 6.77–7.33 (m, 5 H, Ar), 8.54 (brs, 1 H, OH).

Ethyl 4-cyano-5-(3′-hydroxyphenyl)-2-methyl-2-oxazoline-4-carboxylate 6f

HRMS, *m/z*: M$^+$ 274.0936 (calculated for $C_{14}H_{14}N_2O_4$: 274.0953). **6f** *trans*. ^{1}H NMR (200 MHz, [$^2H_6$]acetone, TMS as internal ref.) 1.33 (t, 3 H, *J* = 7.1 Hz), 2.19 (s, 3 H), 4.36 (q, 2 H, *J* = 7.1 Hz), 6.00 (s, 1 H), 6.76–7.90 (m, 3 H, H-3′, H-4′, H-5′), 7.25 (d, 1 H, *J* = 8.2 Hz, H-6′), 8.64 (brs, 1 H, OH). ^{13}C NMR (75 MHz, [$^2H_6$]acetone, TMS as internal ref.) 13.79 (qt, *J* = 128, 2.5 Hz), 14.13 (q, *J* = 131 Hz), 64.40 (tq, *J* = 149, 4.6 Hz), 78.47 (s, C-4), 86.66 (dt, *J* = 152, 4.8 Hz, C-5), 113.67 (dm, *J* = 161 Hz, C-4′), 115.03 (d, *J* = 6.3 Hz, CN), 117.85 (dm, *J* = 161 Hz, C-6′), 118.10 (dm, *J* = 161 Hz, C-5′), 130.73 (d, *J* = 160 Hz, C-2′), 137.34 (dd, *J* = 8.7, 2.5 Hz, C-1′), 158.47 (m, C-3′), 166.64 (m, C-2), 171.79 (qd, *J* = 7.2, 1.7 Hz, CO). **6f** *cis*. Mp = 110–112 °C from CH_2Cl_2. ^{1}H NMR (200 MHz, [$^2H_6$]acetone, TMS as internal ref.) 0.89 (t, 3 H, *J* = 7.2 Hz), 2.21 (s, 3 H), 3.75 (m, 2 H), 6.08 (s, 1 H), 6.76–6.90 (m, 3 H, H-2′, H-4′, H-6′), 7.22 (t, 1 H, *J* = 8.1 Hz, H-5′), 8.64 (brs, 1 H, OH). ^{13}C NMR (75 MHz, [$^2H_6$]acetone, TMS as internal ref.) 13.60 (qt, *J* = 127, 2.7 Hz), 13.90 (q, *J* = 130 Hz), 63.57 (tq, *J* = 150, 4.5 Hz), 76.53 (s, C-4), 88.67 (dt, *J* = 152, 4.6 Hz, C-5), 113.88 (dm, *J* = 159 Hz, C-4′), 117.13 (dd, *J* = 145 Hz, C-6′), 117.25 (dm, *J* = 154 Hz, C-5′), 118.06 (d, *J* = 6.7 Hz, CN), 130.39 (d, *J* = 160 Hz, C-2′), 135.32 (dd, *J* = 8.7, 2.5 Hz, C-1′), 158.23 (d, *J* = 8.6 Hz, C-3′), 164.14 (m, C-2), 172.13 (qd, *J* = 7.3, 1.6 Hz, CO).

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Synthesis of fatty alcohol mixtures from oleochemicals in supercritical fluids†

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Hydrogenation of various types of oleochemicals is a major unit operation in industry. Traditional methods utilize batch, stirred reactor operation resulting in long reaction times and excessive use of catalyst and hydrogen. In this study, reduction of fatty acid methyl esters (FAME) to fatty alcohol mixtures in two different types of supercritical media (H_2/CO_2 and H_2/C_3H_8) were compared using two different hydrogenation catalysts. High and rapid conversions are achieved at the highest experimental temperature (250 °C) and at a hydrogenation mole fraction of 0.25. The described hydrogenation methods has been coupled with an enzymatic-catalyzed transesterification to yield a novel sequential two step synthetic procedure, which permits high fatty alcohol yields to be achieved directly from soybean oil.

Introduction

Fatty alcohols and their derivatives are important in many industrial processes where they are used as raw materials for surfactants and lubricants. A fatty alcohol is, in general defined as a monohydric aliphatic alcohol with six or more carbon atoms. The annual production of fatty alcohols is over 1 million metric tons. Commercially, fatty alcohols are produced by one of three processes: the Ziegler process, the Oxo process or by a high pressure hydrogenation of fatty acids or esters. The latter process is the only process that uses natural fats or oils whereas the two first processes utilize petrochemical feedstocks.[1] Depending on their application, fatty alcohols are divided into subgroups. Thus fatty alcohols having eleven or more carbon atoms are usually called detergent range alcohols because they are used in the detergent industry mainly as sulfate, ethoxylate or ethoxy sulfate derivatives. Fatty alcohols with less than eleven carbon atoms are called plasticizer range alcohols, and they are used as plasticizers and lubricants mainly in the form of ester derivatives.

The conversion of many lipid species to other useful oleochemical compounds can be readily accomplished in supercritical carbon dioxide (sc-CO_2). This is due to the relatively high solubility and diffusivity of these compounds in dense CO_2. Further, the strong pressure dependence of reaction rate constants promotes exact control of the reactions. A large number of chemical reactions have been successfully conducted in supercritical fluids,[2–7] including hydrogenation[8–11] and lipase-based catalysis of oils/fats.[12,13] Further, esterifications, glycerolyses, and hydrolyses of vegetable oils have been performed in sc-CO_2. In addition, hydrolyses of fats/oils can be achieved using subcritical water.[14]

Recently Harrod *et al.*[15–17] and Tacke and co-workers[18,19] have explored the hydrogenation of oleochemicals. These investigators have provided convincing evidence that hydrogenation of fats/oils and oleochemicals is feasible under supercritical conditions, using agents as sc-CO_2 and supercritical propane (sc-C_3H_8). Patents[20,21] have been submitted/issued, claiming the uniqueness of the above processes, although the economic rationale and willingness of industry to accept these unusual approaches is still unknown. Moreover, somewhat unconventional catalysts, as compared to those currently used in industry, were used to perform the hydrogenation in small-scale flow reactors.

In this study, we have extensively investigated the hydrogenation of fatty acid methylesters (FAMES) of soybean oil using mixtures of hydrogen with sc-CO_2 or sc-C_3H_8. A novel experimental approach has been developed using commercially available supercritical fluid extraction (SFE) instrumentation, and the reaction conditions have been optimized for a flow reactor. The derived product mixtures have been characterized using gas chromatography (GC) as well as capillary supercritical fluid chromatography (SFC); the results indicate that

Green Context

This paper demonstrates the feasibility of the continuous hydrogenation of fatty acid methyl esters from vegetable oil resources using a 'green' synthesis approach. The new route is based on supercritical carbon dioxide as an environmentally benign solvent, a lipase catalyst and a chromium-free catalyst for the hydrogenation step. One of the products from the hydrogenation step is methanol and this can be recycled back to the transesterification step. The integration of several cleaner and safer technologies will become increasingly important in future process chemistry. The fatty alcohol mixtures from the above synthesis are potential feedstocks for the industrial synthesis of surfactants or they could be fractionated further to produce higher purity oleophilic alcohols. *JHC*

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† Names are necessary to report factually on available data; however the U.S. Department of Agriculture (USDA) neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may be suitable.

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there are advantages and disadvantages of the use of either the sc-H_2/CO_2 or the sc-H_2/C_3H_8 systems. High yields of saturated alcohols are realized (*ca.* 90% steryl alcohol) at pressures and temperatures above 150 bar and 210 °C, respectively. The reaction utilizes conventional hydrogenation catalysts and has been successfully coupled with enzymatic synthesis of the FAMES in sc-CO_2 to yield a two step, highly efficient reaction sequence for converting vegetable oils to saturated alcohol mixtures.

Experimental

The basic experimental apparatus for studying the hydrogenation of FAMES under supercritical conditions is shown in Fig. 1 The individual gases (fluids) were metered using a Brooks Series 5850E mass flow controller, whose output was fed into a 1000 mL capacity Parr Instruments Co. high pressure, stirred autoclave (Model No. 4501 Parr Instruments Co., Moline, IL) to assure homogeneity. The resultant binary fluid mixture was then compressed to the desired reaction pressure using a Haskel AGT-62/152 gas booster compressor (Haskel Mfg. Co., Burbank, CA) and introduced into the reaction vessel containing either copper chromite catalyst E-406TU (Engelhard Inc., Erie, PA) or a chromium-free catalyst, T-4489 (United Catalysts Inc., Louisville, KY). For the determination of the void volume of the filled reaction cell, the cell was connected to a supercritical fluid chromatograph; void volume was achieved on injection of carbon tetrachloride. For the reactions, the cell was contained in the thermostatted oven of a Speed supercritical fluid extraction unit (Applied Separations Inc., Allentown, PA). The synthesized alcohols were collected in a vial after decompression of the binary fluid mixture through the micro metering valves on the Speed unit. The expanded gas was measured with a gas flow meter. The byproduct methanol was trapped in a condenser. The mass balance was not validated, however, any unconverted methyl esters would show up in the subsequent GC or SFC analysis.

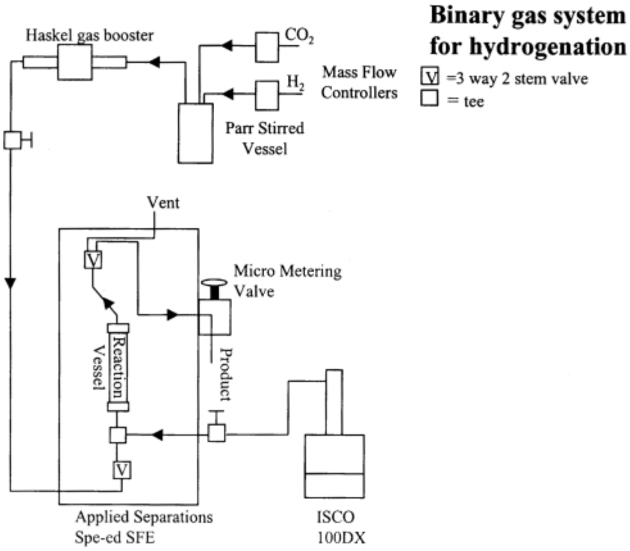

Fig. 1 Reaction system for hydrogenating FAMES to alcohols using binary fluid mixtures of sc-H_2/CO_2 or sc-H_2/C_3H_8.

As shown in Fig. 1, the FAME feedstock was fed into the sc-H_2/CO_2 or sc-H_2/C_3H_8 stream using an Isco Model 100 DX syringe pump (Isco, Inc., Lincoln, NE). The FAME-sc-H_2/CO_2 or sc-H_2/C_3H_8 mixture was then transported over the hydrogenation catalyst contained in one of several small volume reactor vessels (1–4.5 mL cells). For these experiments, a variety of Isco syringe pumps were utilized to deliver reagents (soybean oil, methanol, FAMES) as well as liquefied fluid (CO_2). For the initial hydrogenation studies, a welding-grade CO_2 was used in conjunction with hydrogen Grade 4 (The BOC Group Inc., Murray Hill, NJ) or propane from the same source. In later experiments involving enzymatic synthesis of FAMES, SFC/SFE-Grade CO_2 (Air Products and Chemicals Inc., Allentown, PA) was used and delivered *via* a cooled syringe pump. Soybean oil (refined, bleached, and deodorized) was obtained from Riceland Industries; and the FAME feedstock with the exception of the enzymatically-synthesized product, from either Chemol Company (Chemol Company Inc., Greensboro, NC) or SoyGold 1100 (AG Environmental Products L.L.C., Lenexa, KS).

The system used to study the sequential, two-step reaction conversion of soybean oil to fatty alcohol mixtures coupled an Isco SFX-2-10 extractor module with flanking Isco syringe pumps that were used to deliver the oil, 4 μL min^{-1}, and methanol, 5 μL min^{-1}, respectively into the sc-CO_2 prior to the reactor cell. Transesterification of soybean oil was accomplished using a similar procedure and conditions as described by Jackson and King.[22] Utilizing a pressure of 170 bar and a temperature of 50 °C, a supported enzyme catalyst, isolated from *Candida Antarctica*, Novozym SP 435 (Danbury, CT) contained in a 2.5 mL reaction vessel, was employed as a small tubular reactor for the oil to FAME conversion. The resultant product was then transferred into the apparatus shown in Fig. 1 using sc-H_2/CO_2 to hydrogenate the synthesized FAMES.

Gas chromatographic analysis of the resultant fatty alcohols or by-products, and the starting reactants (FAMES), utilized a HP-1 25 m, 250 μm i.d., 0.25 μm film thickness column contained in a Hewlett Packard Model 6890 gas chromatograph (Little Fall, PA). The supercritical fluid chromatographic (SFC) analysis of product/reactant mixtures from the enzyme synthesis step was accomplished using a Dionex Series 600 SFC (Dionex Inc., Salt Lake City, UT) containing a SB-Methyl-100, 10 m, 50 μm i.d., 0.25 μm film thickness column (Dionex Inc., Salt Lake City).[23]

The experimental parameters that were investigated in this study are listed in Table 1. Both types of hydrogenation catalysts were tested with the sc-H_2/CO_2 and sc-H_2/C_3H_8 mixtures over a pressure range of 150–250 bar and a temperature range of 210–250 °C. Here all solvents are above their critical points. The mole fraction of hydrogen in the sc-CO_2 and sc-C_3H_8 ranged from 0.10–0.25. Residence times in the reactor vessels ranged from 4–9 s, while FAME feed for the

Table 1 Range of experimental conditions investigated utilizing the system in Fig. 1 for hydrogenation of FAMES to alcohols

Fluid	Catalyst	*P*/bar	*T*/°C	Mole fraction (H_2)	Residence time/s	Substrate flow/μL min^{-1}
CO_2	Copper chromite	150–250	210–250	0.10–0.25	4–9	25–50
CO_2	Chromium free	150–250	210–250	0.10–0.25	4–9	25–50
Propane	Copper chromite	150–250	210–250	0.10–0.25	4–9	50–250
Propane	Chromium free	150–250	210–250	0.10–0.25	4–9	50–250

sc-H_2/CO_2 system was 25–50 and 50–250 μL min^{-1} for the sc-H_2/C_3H_8 mixtures. Critical parameters and densities were calculated using Isco SF Solver program (Isco).

The experiments were done in a 2^{5-1} factorial design including four center points resulting in a total of 20 experiments. In a typical run, after 20 min temperature equilibration using a continuous gas flow, the substrate pump was started and allowed to run an additional 20 min. Finally a sample was collected during a 20 min period. The evaluation of the optimum reaction conditions was made by using Codex (Sum-it System, Solna, Sweden).

Results and discussion

Scouting experiments showed that incomplete reaction only resulted in saturation of the double bonds of the fatty acid chain together with the production of a small amount of fatty alcohols. When the reaction, on the other hand, was allowed to go too far, extensive *n*-alkane formation resulted.

For the sc-H_2/CO_2 as well as for the sc-H_2/C_3H_8 system only two of the variables were found to have a significant impact on the hydrogenated product purity. These were temperature and hydrogen content of the fluid. These variables should be kept at a high level, as is clearly evident from the response surfaces shown in Figs. 2(*a*) and (*b*). The substrate flow rate, pressure and residence time were not found to have a significant effect on the hydrogenation process in the investigated experimental domain. As an example, a response plot obtained with the chromium free catalyst and sc-H_2/C_3H_8 mixtures is shown in Fig. 2(*b*). When the hydrogenation was performed under optimal conditions the two catalysts gave similar results. The catalyst was used multiple times.

The response surface for the sc-H_2/C_3H_8 system indicates that high alcohol conversions can be accomplished also when using lower mole fractions of hydrogen in propane than for the corresponding sc-H_2/CO_2 system (*ca.* 50%). Response surfaces for the copper chromite catalyst, Figs. 2(*c*) and (*d*), follow a similar pattern but the trends are not as clear. At high mole fractions of H_2 the sc-H_2/CO_2 system is superior to the sc-H_2/C_3H_8 system. However, at low mole fractions of H_2, both the sc-H_2/CO_2 and the sc-H_2/C_3H_8 systems give approximately the same yield, *i.e.*, 80% conversion. This indicates the importance of catalyst selection for the overall yield and the reaction conditions that are required.

The gas chromatographic profiles of the hydrogenated product mixtures derived from the reaction in the sc-H_2/CO_2 and sc-H_2/C_3H_8 systems are shown in Figs. 3(*a*) and (*b*). Peaks were tentatively identified by comparisons with the retention time of standard compounds. In Fig. 3(*a*), the flame ionization detector (FID) response indicates a high degree of conversion yield (97.2%) for both methods used to prepare the hydrogenated fatty alcohols (steryl and palmityl alcohols) from soybean oil. Only trace levels of unconverted FAMES remain. However, Fig. 3(*b*) which shows the composition of the product obtained with the sc-H_2/C_3H_8 system, indicates not only the appearance of the fatty alcohols, but also significant amounts of C_{16} and C_{18} *n*-alkanes as by-products. This has been observed also by other researchers.[23,24] In this case, the two alcohols constitute 95% of the product, while the *n*-alkane components were 4.6% of the total product yield. Both product mixtures were generated at 250 bar, 250 °C, a hydrogen mole fraction of 0.25 and a residence time of 9 s, using chromium-free catalyst.

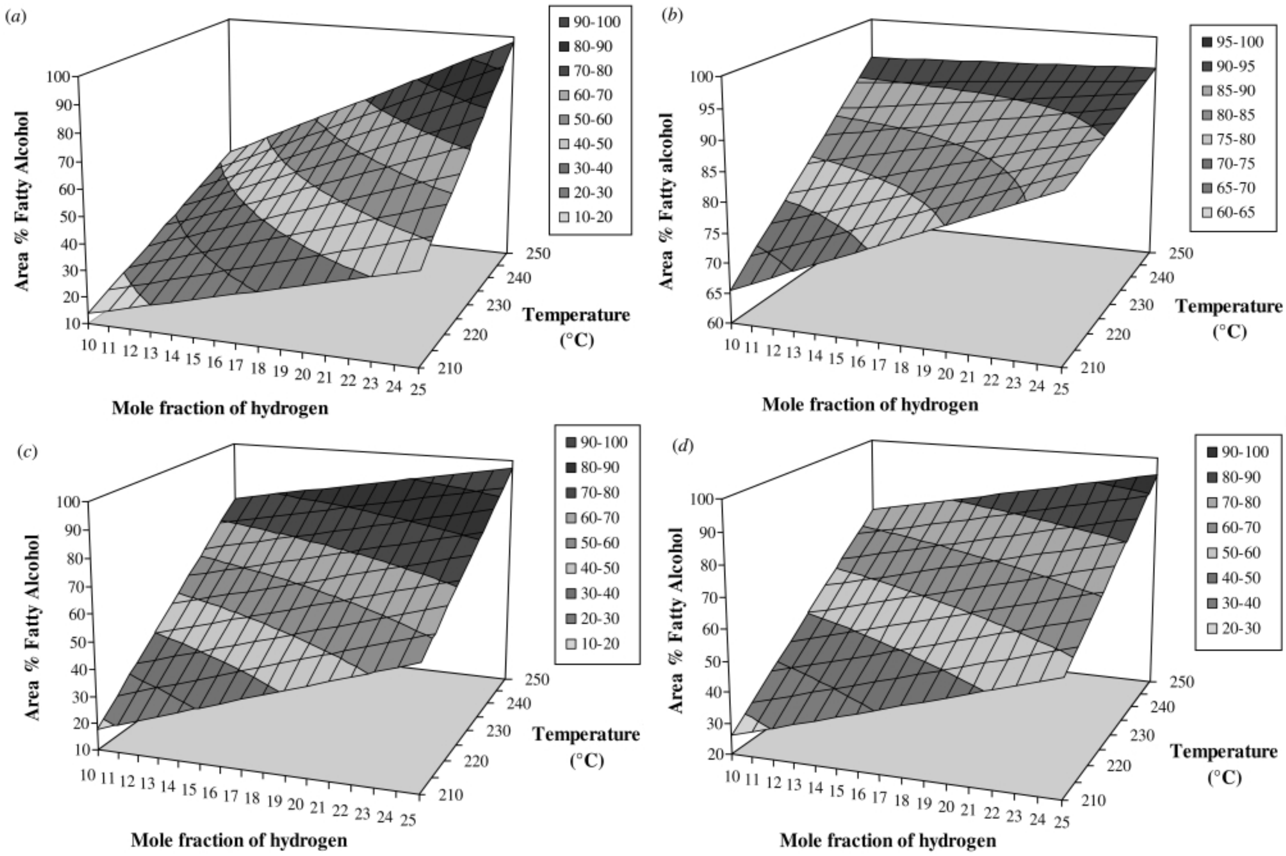

Fig. 2 (*a*) Response surface plot for production of fatty alcohols using chromium-free catalyst in sc-H_2/CO_2. Approximate residence time, 5.5 s; substrate flow, 37.5 μL min^{-1}; pressure, 200 bar. (*b*) Response surface plot for production of fatty alcohols using chromium-free catalyst in sc-H_2/C_3H_8. Approximate residence time, 5.5 s; substrate flow, 150 μL min^{-1}; pressure, 200 bar. (*c*) Response surface plot for production of fatty alcohols using copper chromite catalyst in sc-H_2/CO_2. Approximate residence time, substrate flow and pressure as in Fig. 2(*a*). (*d*) Response surface plot for production of fatty alcohols using copper chromite catalyst in sc-H_2/C_3H_8. Residence time, substrate flow and pressure as in Fig. 2(*b*).

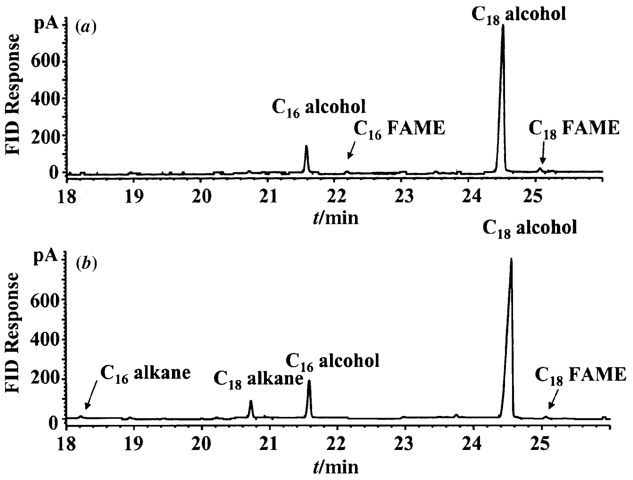

Fig. 3 (*a*) GC profile of products from critical fluid hydrogenation (sc-H_2/CO_2) of FAMES using chromium-free catalyst. Reaction conditions: pressure 250 bar, temperature 250 °C, mole fraction of H_2 0.25, residence time 9 s; substrate flow rate 50 μL min^{-1}. (*b*) GC profile of products from critical fluid hydrogenation (sc-H_2/C_3H_8) of FAMES using chromium-free catalyst. Reaction conditions: pressure 250 bar, temperature 250 C, mole fraction H_2 0.25, residence time, 9 s; substrate flow rate 250 μL min^{-1}.

Using copper chromite catalyst for the two binary gas mixtures under basically the same conditions yielded a similar result.

Thus there are tradeoffs in employing the sc-H_2/CO_2 or sc-H_2/C_3H_8 system; the first system allows the highest potential conversion to alcohols to be achieved, while the second binary fluid mixture (H_2/C_3H_8) permits a higher throughput. The rate of conversion of FAMES to alcohols is higher for the sc-H_2/C_3H_8 mixture than for the sc-H_2/CO_2 binary fluid. For example, 3 times more alcohol can be synthesized in the sc-H_2/C_3H_8 mixture in 2/3 of the time as compared to what can be accomplished under similar conditions in the sc-H_2/CO_2 system.

Fig. 4 illustrates the GC product mixture obtained when using enzymatic catalysis to form the FAMES from soybean oil followed by a hydrogenation over a chromium-free catalyst. This was accomplished using the complex system shown in Fig. 5. Here the hydrogenation step uses the identical experimental apparatus previously noted for the critical fluid hydrogenations (Fig. 1). A multiple syringe pump system (A–D) was used to deliver the appropriate amounts of CO_2 (A–B), soybean oil (C), and methanol (D) into the extraction (reaction) cell of an Isco SFX-2-10 module (E), containing the Novozym SP 435 catalyst. The resultant product from the transesterification (Fig. 4) was then fed into the flow stream as designated in the hydrogenation sequence of the overall reaction. High conversion to alcohols, 96.5% yield, with only traces of the original FAMES and *n*-alkanes were detected in the chromatogram (Fig. 4). This demonstrates that the two-stage reaction sequence performs well when using the same conditions as applied for the reactions leading to the product composition in Fig. 3(*a*). The conversion of the soybean oil over Novozym SP 435 was examined using capillary SFC. The reaction was relatively complete; C_{16}, C_{18} FAME and only minor amounts of mono-, di- and tri-glyceride appeared in the chromatogram as shown in Fig. 6.

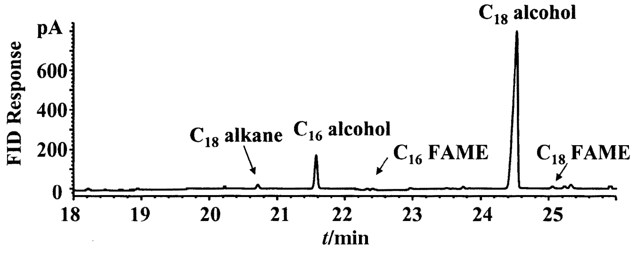

Fig. 4 GC profile of products from SFR (transesterification)/ SFR(hydrogenation-sc-H_2/CO_2) of soybean oil. Reaction conditions for the transesterification step: pressure 170 bar, temperature 50 °C; oil flow rate 4 μL min^{-1}, methanol flow rate 5 μL min^{-1} CO_2 flow rate 1 mL min^{-1}. Reaction conditions for the hydrogenation step: pressure 250 bar, temperature 230 °C, mole fraction of H_2 0.25, residence time 9 s.

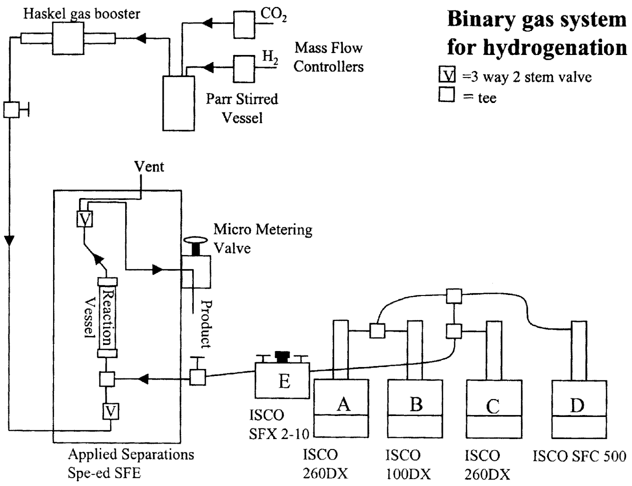

Fig. 5 Reaction system for performing transesterification of soybean to FAMES followed by critical fluid hydrogenation reaction to produce fatty alcohol mixtures.

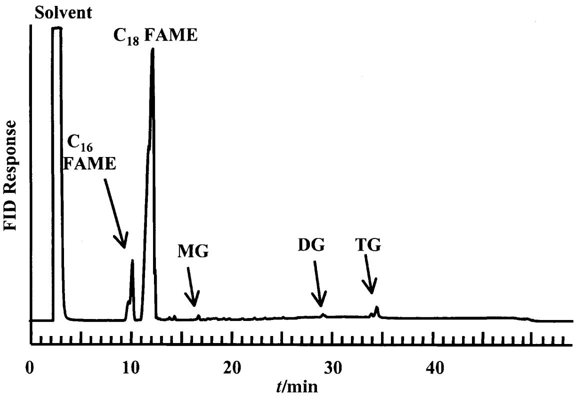

Fig. 6 SFC profile of the transesterification step using Novozym SP 435. MG, mono-glyceride; DG, di-glyceride; TG, tri-glyceride.

Conclusions

Reaction in supercritical propane resulted in the highest production of fatty alcohol per time unit. However, when using propane, significant amounts of C_{16} and C_{18} *n*-alkane were formed as by-products while virtually no alkanes were formed in carbon dioxide, which is a distinctive advantage. Further, carbon dioxide is more environmental compatible and non-flammable. Moreover, the enzymatic catalysis followed by hydrogenation gave a high yield, only traces of FAME and alkanes were present in the product. The results in this study demonstrate the feasibility of continuous hydrogenation of fatty acid methyl esters from vegetable oil resources using a 'green' synthesis approach.

Our study was accomplished using analytical scale equipment and such 'green' reagents as carbon dioxide, a lipase catalyst, and a chromium-free catalyst for the hydrogenation step. For the hydrogenation step, the rapid conversion rate of the FAME substrate suggests a potentially high production rate if the process is scaled up. It is interesting to note that these 'supercritical' hydrogenations are dependent on the choice of catalyst with respect to optimization of product yield and distribution. Since one of the products from the hydrogenation step is methanol, there is a possibility to recycle this alcohol back to the transesterification step to be utilized as a reactant for forming more FAMES.

FAMES as opposed to neat fatty acids should be viewed as a key synthetic starting material for the synthesis of oleochemicals in critical fluid media. This is because they minimize corrosion of reactor materials and attrition of the catalyst. The resultant fatty alcohol mixtures from the above reaction sequence are potential feedstock for industrial synthesis of surfactants.[25] In addition, they could be fractionated further, perhaps using supercritical fluid fractionation, to produce even higher purity oleophilic alcohols.

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Process intensification: spinning disc reactor for condensation polymerisation

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This paper describes the performance of a thin film reactor in the form of a spinning disc reactor which may be used for continuous condensation polymerisation of esters. Test results suggest that it may be possible to significantly enhance the rate of polymerisation by addressing the mass transfer and mixing limitations thereby performing the reaction at its inherently faster kinetic speed. This technology may provide an opportunity for the intensification of condensation polymerisation processes.

Introduction

The melt polymerisation of polyesters is a mass transfer limited process. The volatile condensation product must diffuse out from the viscous melt into a controlled atmosphere, usually vacuum or nitrogen. The influence of the diffusional process on the reaction kinetics have been studied by Pell and Davis[1] and modelled using the Higbie penetration theory by Secor.[2] Pell and Davis[1] found that the rates of polycondensation reactions in thin static films of monomer reactants under nitrogen or vacuum atmosphere were strongly dependent on the diffusivity of the condensation product through the melt and hence the film thickness. More recently, it was shown that liquid crystalline polyesters could be produced at much higher rates of polymerisation in thin films of polymerising material than in bulk polymerisation as a result of enhanced mass transfer in the former.[3] In a separate extensive study with thin films of monomer, very high molecular weights have been achieved in extremely short reaction times (1–20 s) using film thicknesses in the range 1–100 μm during condensation polymerisation.[4] Prior to that work, a process was patented by DuPont which gave rapid polymerisation rates in thin polyester films.[5] In spite of the above mentioned studies the reactor technology used in industry is still based on the conventional batch technology which has modest mass transfer and mixing characteristics. The residence times are high, often in excess of 10 h and the product quality is rather poor.

Based on the published information on thin static film polymerisation of polyesters, we have designed an intensified thin film spinning disc reactor (SDR) which may be used for the continuous polymerisation of polyesters. The spinning disc reactor produces thin highly sheared films which have been shown to provide good heat and mass transfer as well as improved mixing characteristics.[6–9] Although previous tests have made use of extremely thin films, such film thicknesses would obviously be difficult to maintain in a continuous reactor. Therefore in a SDR we have aimed at using thicker films of 100–200 μm but with transport rates in the liquid and gas phases significantly higher than those used by previous workers.

It is, therefore, our intention to present in this paper a background for the chemistry of polyesterification followed by a review of the various types of reactors which have been used in the production of polyesters. The use of a novel spinning disc reactor for condensation polymerisation will be described and results of experimentation with the SDR will be presented and discussed.

Polyester chemistry

Esters are the products of a condensation reaction between an alcohol, denoted by R′–OH and an organic acid, denoted by RO–OH. The units R and R′ are aliphatic and/or aromatic groups. The condensation reaction yields ester and water:

$$\mathrm{R'{-}OH + RO{-}OH \rightarrow R'{-}O{-}OR + H_2O}$$

Similarly, a polybasic acid and a polyhydric alcohol can be used in a condensation reaction to give a polyester, *e.g.* a dibasic acid with a dihydric alcohol:

$$\underset{\text{dihydric alcohol}}{\mathrm{HO{-}R'{-}OH}} + \underset{\text{dibasic acid}}{\mathrm{HO{-}ORO{-}OH}} \rightarrow \mathrm{{-}R'{-}O{-}ORO{-}O{-}R'{-}} \quad \begin{matrix} + & + \\ \mathrm{H_2O} & \mathrm{H_2O} \end{matrix}$$

The acid can sometimes be used in the anhydrous form, where water has already been removed from the molecule, *e.g.* maleic anhydride.

Green Context

The rate of polycondensation reactions such as those used in the manufacture of polyesters are strongly dependent on the rate of diffusion of the condensation product from the viscous melt. Current manufacturing processes are based on batch technology with associated modest mass transfer and mixing characteristics and long residence times. These processes are ideal candidates for process intensification where the goal is to miniaturise the plant without reducing capacity. It has already been demonstrated that high molecular weight polymer products can be achieved after short reaction times using thin films and here the concept is taken further to the use of spinning disc reactors. These enable the formation of thin, highly sheared films that are known to give good heat and mass transfer characteristics. In this way significant increases in the rates of polymerisation have been achieved. *JHC*

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Unsaturated polyesters are produced by the condensation of dibasic acids and dihydric alcohols, in which one or both of the monomers are unsaturated *i.e.* a double bond is present in the alcohol or the acid. A typical example is the reaction between ethylene glycol and fumaric acid:

$$\text{HO–OC–CH=CH–CO–OH} + \text{HO–CH}_2\text{–CH}_2\text{–OH} \rightarrow \text{–OC–CH=CH–CO–O–CH}_2\text{–CH}_2\text{–O–} + \text{H}_2\text{O}$$

The double bond in the fumaric acid makes the polyester unsaturated. The presence of the double bond allows the unsaturated polyester to be further reacted with a reactive monomer to cross link the polymer chains, as required for some applications. This process is known as copolymerisation or curing. The choice of reactive monomer is important since it may impart special characteristics such as heat resistance to the polymer.[10]

The copolymerisation process is carried out using an initiator, usually a peroxide.[10] These initiators open the double bond in the unsaturated acid by a free radical mechanism to allow the insertion of the reactive monomer.

Saturated polyesters are produced by the condensation reaction of saturated monomers, and so no copolymerisation using a reactive monomer can be performed. If a saturated dihydric alcohol is reacted with a saturated dibasic acid, then a high molecular mass, linear polymer molecule is formed, which has no cross linking. Cross linked saturated polyesters can be obtained by using monomers with more than two functional groups, *e.g.* trifunctional glycerol: $HOCH_2CH(OH)CH_2OH$.

For the production of unsaturated polyesters, it is usual to have the acid as the unsaturated monomer. To obtain better solubility in the reactive monomer for the copolymerisation stage, a mixture of saturated and unsaturated acid is often used, such as maleic and phthalic acids. The acid can also be used in the form of a dimethyl ester, under which conditions transesterification occurs. The difunctional alcohol replaces the monofunctional alcohol, forming the polyester and also leads to the formation of methanol. The alcohol used is usually a glycol, such as propylene glycol or butylene glycol. An alcohol with a functionality greater than two will give cross linking, which gives a stronger polymer, but will also cause a higher viscosity in the reaction mixture (melt) and lower compatibility with the reactive monomer/solvent. The feed is usually approximately in stoichiometric proportions with *ca.* 5% excess of alcohol.[11]

The polycondensation reaction is an equilibrium driven reaction and can be represented by the equilibrium constant K given by eqn. (1),

$$K = \frac{[\text{polyester}]\,[\text{water}]}{[\text{alcohol}]\,[\text{acid}]} \qquad (1)$$

where $K \approx 10^{12}$.

Therefore, the reaction can be driven towards completion by the removal of water from the melt. However, the high viscosity resulting from the polymerisation makes this difficult. Technological advances in the production of polyester has mainly concentrated on removing water from the melt.

At present, the process is almost invariably carried out batchwise in a large stirred tank reactor at atmospheric pressure.[12] The monomer mixture is heated from 50 to > 100 °C mainly by the reaction exothermicity in the prepolymer stage and leaves only 3–5% free monomer. Then, the melt is heated to 150 °C, where it starts to reflux. The temperature is slowly raised over the batch time towards 280 °C. If the melt is heated too quickly, then the alcohol can react with the unsaturated acid by adding over the double bond, which must be avoided.

The batch reaction usually takes 15–18 h[11] to reach the required acid number of < 50 mg KOH/g polymer[13] with a simple inert gas blanket. The batch time can be reduced by increasing the rate of water removal. The vapour is fractionally condensed and the organic phase returned to the melt.

It is known that the rate of change of acid number is proportional to the rate of de-watering .[12] Also, the following relationship [eqn. (2)] holds for condensation polymerisation:[12]

$$x \propto (m_{H_2O})^{-1/2} \qquad (2)$$

where x = degree of polymerisation and m_{H_2O} = mass fraction of water in the melt.

Bubbling the inert gas through the melt, or using an aromatic hydrocarbon, such as xylene, to increase the vapour pressure of water can reduce the processing time by 30–50%.[12] An extra advantage of using xylene is that the polyester is often delivered dissolved in xylene, and so the xylene used to aid de-watering need not be removed. Complete elimination of water is not possible owing to the melt being slightly soluble in water and water always runs back off the condenser fittings.

Operating under vacuum can also be used to increase de-watering. Also, it has been found that:[12]

$$\text{Rate of change of acid number} \propto 1/P \qquad (3)$$

where P is the operating pressure.

The use of vacuum conditions throughout the batch can lead to other molecular structures forming, and so it is usual to operate at atmospheric conditions as much as possible.[12] Once the acid number has reached 50 mg KOH/g polymer, the use of vacuum can allow acid numbers of 25–30 mg KOH/g polymer to be reached. It is usual to sequence these methods for de-watering to obtain the optimum rate of reaction.

The batch must be terminated close to the tolerance on acid number or hydroxyl number or else the batch will be ruined with no chance of recycling. The final product will have a range of molecular weights. The tighter the molecular weight distribution, the better the polymer. The number average molecular mass can be found from empirical formulae [eqns. (4) and (5)][14,15]

$$M_n = \frac{112220}{\text{AV} + \text{HN}} \qquad (4)$$

or

$$M_n = \frac{56000}{\text{AV}} \qquad (5)$$

where M_n = number average molecular mass (g mol^{-1}), AV = acid number of the melt (mg KOH/g polymer) and HN = hydroxyl number of the melt (mg KOH/g polymer).

Typically, the final molecular mass for the polyester will be *ca.* 1200–1600 g mol^{-1}. Once the required acid value is reached, the batch is cooled to below 150 °C, usually to *ca.* 90 °C and reacted in the copolymerisation stage, referred to as finishing. The polyester is mixed with a reactive monomer, usually styrene, to give 35–40% reactive monomer in the final polymer, and is reacted in a wiped surface contactor at temperatures below 70 °C to prevent gelling.[12] Higher concentrations of styrene will lead to the production of polystyrene. Metal acetate catalysts, such as zinc, sodium or lead acetate, can be used, but cause colourisation of the product, and so they are not normally used. The copolymerisation stage uses a free radical mechanism for reaction, and so a peroxide, *e.g.* benzoyl peroxide is used to promote the formation of free radicals. After the copolymerisation, the polyester has a molecular mass of 2000–14000 g mol^{-1}, and each polyester chain has between one and three styrene units linking it with another chain.[10]

The Bivolak reactor, made by Sumitomo Heavy Industries uses two counter rotating shafts, with a speed ratio of 2 : 1.[16] It is claimed to increase the condensation rate of PET by a factor of two over conventional helical ribbon mixers. The Bivolak is claimed to be able to handle melts with a viscosity of a few thousand poise, temperatures up to 350 °C and pressures up to 4 Barg.

A reactor for the production of condensation polymers, such as polyesters, must have good mass and heat transfer. The reactive groups in the melt must be contacted at a high rate for reaction, and the reaction by-product, water, needs to be removed from the melt to drive the reaction to a good overall conversion. Since the rate determining step in the removal of water from the melt is in the liquid phase,[17] a high degree of mass transfer in the film is required. Similarly, good heat transfer is required to allow the batch to have a temperature profile which approaches the optimum. A good rate of reaction is required at the same time as suppressing side reactions.

The molecular weight distribution of the polymer affects its properties. The tighter the distribution, the more uniform the properties of the polymer, and so the higher the polymer quality. A large batch tank reactor, which only has reaction at the gas-liquid interface,[16] will inevitably give a very wide molecular weight distribution because there is no control of the reaction time distribution of the melt. A good condensation polymer reactor should have a uniform reaction time distribution.

Another requirement of this, and any, reactor is that it must be safe. A large batch tank reactor of flammable polymer melt represents a potentially large accident hazard, and any incident involving the reactor would usually be major. Reducing the inventory of flammable material in the reactor at any one time, without reducing the overall capacity of the reactor would greatly increase intrinsic safety and would, therefore, be preferred.

Spinning disc reactor

A thin film spinning disc reactor (SDR) has been developed and is currently being studied by research workers at the Process Intensification & Innovation Centre (PIIC) in Newcastle. The SDR produces thin highly sheared rippling films as shown in Figs. 1 and 2 by using the centrifugal force which is produced on rotating surfaces. Recent studies have indicated that the fluid dynamics within these films result in significant enhancement in the heat and mass transfer rates.[7,8] A high degree of mixing may also be obtained owing to the presence of numerous surface waves in the film. Grooves on the disc have been shown to promote turbulence in the film, and so can further improve the transport characteristics of the thin film flow as suggested by previous studies.[7]

Fig. 1 Surface waves on a smooth rotating disc surface.

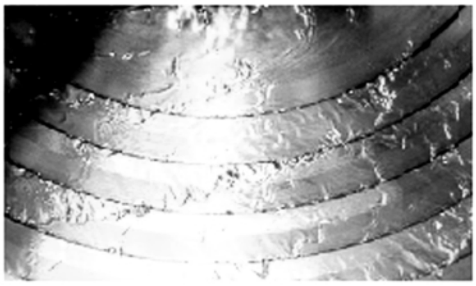

Fig. 2 Surface waves on a grooved rotating disc surface.

The residence time distribution of the melt on the disc should be reasonably uniform which would result in a more uniform molecular mass distribution than achieved in a large conventional stirred tank reactor. With a thin film of melt on the disc, the volume of reaction mixture in the system at any one time will be low which will give a high degree of intrinsic safety.

Many chemical engineering systems show an effect due to gravity. This is true of thin film flow, where the film thickness is inversely proportional to the applied force in the direction of the flow. Therefore, a thinner film of fluid can be obtained by increasing the force applied, which will give increased mass transfer in the film owing to the small distance through which diffusion has to occur. However, this is of no immediate use because on earth, the force on a system in the vertical axis is limited to that of terrestrial gravity. The spinning disc concept is an attempt to take advantage of the effects of elevated gravitational force to achieve the aims of the process intensification philosophy. It is important, at this stage, to consider the hydrodynamics of thin film flow characteristic of rotating surfaces.

The general Navier–Stokes equations, presented in the Appendix, have been simplified by a number of workers to obtain an adequate model describing the flow on the rotating disc.[18,19] The following assumptions have been considered in their analysis:

1. The flow of liquid in any direction on the disc is steady so that

$$\frac{\partial v_r}{\partial t} = 0, \frac{\partial v_\theta}{\partial t} = 0, \frac{\partial v_z}{\partial t} = 0$$

2. The influence of gravity, surface tension and interfacial shear with the surrounding medium are not important which means that the terms involving the g components disappear.
3. The pressure is everywhere constant.
4. Since the flow is symmetric about the axis of rotation, there is no variation of velocity in the angular direction,[19] *i.e.*

$$\frac{\partial\ v_r}{\partial\theta} = 0, \frac{\partial\ v_\theta}{\partial\theta} = 0, \frac{\partial\ v_z}{\partial\theta} = 0$$

5. Since the film thickness δ is much smaller than the corresponding radius r, it can be assumed that $v_z << v_r$ or v_θ and $\frac{\partial}{\partial_z} >> \frac{\partial}{\partial_r}$ [18,19]

The simplified set of Navier–Stokes equations obtained on implementation of the above assumptions can be expressed as:

$$-\frac{v_\theta^2}{r} = \nu\frac{\partial^2 v_r}{\partial z^2} \tag{6}$$

$$v_r\frac{\partial v_\theta}{\partial r} + \frac{v_\theta v_r}{r} = \nu\frac{\partial^2 v_\theta}{\partial z^2} \tag{7}$$

where ν is the kinematic viscosity.

A simple centrifugal model can be developed by applying the following assumptions to the simplified Navier–Stokes [eqns. (6) and (7)].

1. The radial velocity component, v_r, is negligibly small compared to the angular velocity v_θ.
2. The angular rate of rotation of the liquid is equal to the rate of rotation of the disc at all radii so that $v_\theta = r\omega$.

The above considerations leaves only eqn. (6) as the basis of the centrifugal model, which essentially represents a simple balance between the centrifugal force and the opposing viscous forces in the radial direction.

Substituting for $v_\theta = r\omega$, where ω is the angular velocity, eqn. (6) becomes:

$$-\omega^2 r = \nu\frac{\partial^2 v_r}{\partial z^2} \tag{8}$$

The radial velocity profile across the thin film on the rotating disc can be obtained by integration of eqn. (8) subject to the boundary conditions:

at $z = 0$ $v_r = 0$ (condition of 'no slip' at the disc surface)

at $z = \delta \dfrac{\partial v_r}{\partial z} = 0$

(condition of zero shear at the free surface of the film).

Thus,

$$v_r = \frac{\omega^2 r}{v}[\delta z - (z^2/2)] \qquad (9)$$

where δ is the thickness of the film.

Eqn. (9) predicts that the radial velocity follows a parabolic path across the film thickness with maximum velocity at the free surface at a given radius.

Using the result for the velocity distribution in the film, the average radial film velocity can be computed as:

$$\bar{v}_r = \frac{1}{\delta}\int_0^\delta v_r \mathrm{d}z = \frac{\omega^2 r \delta^2}{3v} \qquad (10)$$

The average film velocity can also be expressed in terms of the volumetric flowrate Q per unit area of cross-section available for flow:

$$\bar{v}_r = \frac{Q}{2\pi r\delta} \qquad (11)$$

An expression for the film thickness as a function of the system parameters is then formulated from eqns. (10) and (11)

$$\frac{Q}{2\pi r\delta} = \frac{\omega^2 r \delta^2}{3v}$$

which, on rearrangement, yields:

$$\delta = \left(\frac{3vQ}{2\pi\omega^2 r^2}\right)^{1/3} \qquad (12)$$

Setting $\mathrm{Re} = \dfrac{2Q}{\pi v r}$, the film thickness can also be written in the form:[19]

$$\delta\left(\frac{r\omega^2}{v^2}\right)^{1/3} = 0.909\ \mathrm{Re}^{1/3} \qquad (13)$$

The above expression is analogous to the derivation obtained based on Nusselt's theory[20] for fully developed laminar flow down inclined surfaces with the acceleration due to gravity g has been replaced by the centrifugal acceleration $r\omega^2$. Nusselt's equation can be expressed as:[21]

$$\delta\left(\frac{g}{v^2}\right)^{1/3} = 0.909\ \mathrm{Re}^{1/3} \qquad (14)$$

The mean residence time of the film between two radial positions on the disc can be calculated from eqn. (10). Thus:

$$\bar{v}_r = \frac{dr}{dt} = \frac{\omega^2 r\delta^2}{3v}$$

Substituting for δ from eqn. (12), we have, after simplification:

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \left(\frac{\omega^2 Q^2}{12\pi^2 v}\right)^{1/3} r^{-1/3} \qquad (15)$$

This equation is integrated within the limits given below:

$$t = 0,\ r = r_\mathrm{i}$$
$$t = t_\mathrm{res},\ r = r_\mathrm{o}$$

where r_i is the radial distance of the inlet from the centre of the disc r_o is the radius at exit. The resulting expression for the residence time t_res is then obtained as:

$$t_\mathrm{res} = \left(\frac{81\pi^2 v}{16\omega^2 Q^2}\right)^{1/3}(r_\mathrm{o}^{4/3} - r_\mathrm{i}^{4/3}) \qquad (16)$$

The mean residence time and the film thickness are the two most important parameters which characterise the hydrodynamics of fluid flowing on a horizontal rotating disc. On inspection of eqns. (12) and (16), it is found that these two system variables are controlled by the rotational speed ω. An increase in the speed of rotation translates into shorter residence times and thinner films which are very likely to affect the transport properties of the film. On this basis, the rotational speed is a critical parameter which needs to be carefully optimised to achieve the best heat and mass transfer and mixing characteristics on the spinning disc. Also, as explained by Brauner and Maron,[22] the creation of numerous surface waves will also play an important role in the enhancement of the heat and mass transfer rates.

Experimental

A schematic diagram of the thin film spinning disc reactor (SDR) used in the study can be seen in Fig. 3. The reactor set-up is shown in Fig. 4. The SDR consists of a grooved brass disc 360 mm in diameter (Fig. 5), supported by a rotating shaft and driven by a 2 kW electric motor. The geometry of the grooves is shown in Fig. 6. A high temperature bearing system was used and stationary radiant heaters placed under the rotating disc were used for heating the reactor surface. The brass disc was 1 cm thick and had 16 thermocouples embedded at several locations for monitoring the reactor surface temperature. The temperature data was transferred to the data logger *via* a slip ring assembly located at the base of the reactor. The reactor housing contains windows and has provision for conveying the hot pre-polymer onto the centre of the reactor surface. The pre-polymer feed system was also heated in order to prevent the pre-polymer from solidifying in the feed tube. The walls of the reactor housing adjacent to the reactor surface were contacted with a water-cooled collector trough. The top of the reactor was also connected to a condenser.

Reactions involving preparation of two types of unsaturated polyesters from different monomers (reactions I and II) and a saturated polyester (reaction III) were investigated in the SDR. Several batch runs were performed for reactions I and III prior to the tests in the SDR so as to obtain batch calibration profiles suitable for benchmarking the SDR performance. Unsaturated

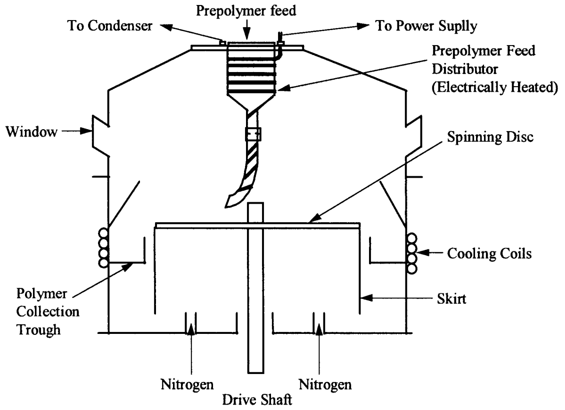

Fig. 3 Schematic of spinning disc reactor (SDR).

Fig. 4 Spinning disc reactor set-up.

Fig. 5 Grooved disc surface.

polyester prepolymers from reaction II were supplied as such at different molecular weights. The reactions were carried out in glass vessels similar to those used in the prepolymer stage of a spinning disc run which is described in more detail below. As the reaction was extremely sensitive to temperature, it was also intended to obtain reproducible exotherms for the batch polymerisations. The temperature was recorded at 5 min intervals and *ca.* 5 ml of sample were taken every 10 min by a pipette through the vertical arm of the vessel. The samples were crash-cooled in cold water to stop any further reaction. Each sample was then prepared for analysis as described below.

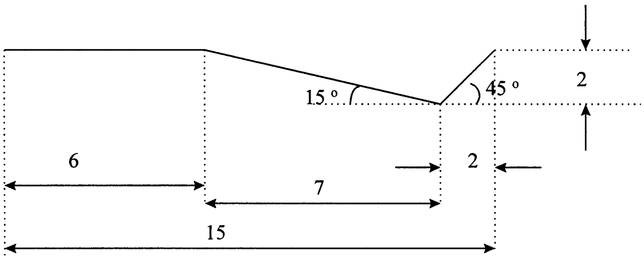

Fig. 6 Normal groove geometry on the rotating disc surface.

The experimental procedures for the polymerisation of both unsaturated and saturated polyesters using the SDR were the same except for the difference in the processing temperatures. A typical spinning disc run was carried out in two stages: (1) pre-polymer stage and (2) spinning disc stage.

Pre-polymer stage

In the first unsaturated polyesterification (reaction I), maleic anhydride and ethylene glycol in the ratio of 1.437 : 1 by weight,[10] (10% molar excess of the glycol), were heated in an electrically heated standard glass vessel provided with paddle mixers. Heating of the reagents was carried out in a controlled manner so that the monomers are taken through various temperature stages up to a maximum of 220 °C. The top end of the reactor was connected to a condenser and nitrogen was injected into the reaction system through a side opening. Using the above mentioned recipe, prepolymer having a desired acid value was prepared in the glass apparatus. The acid value was estimated from the batch calibration curve generated from the batch runs. Having obtained the desired acid value the pre-polymer was introduced on to the disc surface for the final stage operation.

In the second unsaturated polyesterification reaction (reaction II), two different prepolymers of an unsaturated polyester having molecular weights M_w of 620 and 2600 were supplied and only required preheating with stirring in the batch reactor to an operating temperature of 35 °C for the low viscosity prepolymer and to *ca.* 50 °C for the high viscosity pre-polymer.

For the saturated polyesterification (reaction III), a glycol (G), a saturated acid or anhydride (A) and an alcohol (OH) were mixed in molar ratios of 1 : 2 : 2 with a 10% excess volume of the glycol component to account for possible losses. The mixed components were preheated in a standard glass vessel on a heating plate to the operating temperature of 180 °C. Agitation was provided by a magnetic stirrer. Water was allowed to flow at a reasonable rate through the condensers. A moderate flow rate of nitrogen was first bubbled through the mixture to remove any dissolved oxygen; the injection point of the gas was then moved just above the surface of the mixture to provide an inert atmosphere. Once the temperature reached 180 °C in the batch mixture, the stop clock was started. Samples were collected at intervals of 10 min until the selected time for the end of the batch reaction was reached. Prepolymer with a desired acid value was thus prepared before pouring into the SDR.

Spinning disc stage

For the unsaturated polyesterification (reaction I) starting from maleic anhydride and ethylene glycol, the grooved spinning disc surface was maintained at 200 °C. The pre-polymer flow rate was estimated to be *ca.* 50 cm^3 s^{-1} when prepolymer was poured onto the disc *via* gravity and the disc rotational speed was set at 1000 rpm.

For tests using the supplied unsaturated polyester prepolymers (reaction II), the disc temperature was varied between 180 and 300 °C with disc speeds in the range 50 to 500 rpm.

All tests for the saturated polyesterification (reaction III) were performed with the disc heated to *ca.* 180 °C and rotating at 400 rpm.

As soon as the pre-polymer melt came in contact with the disc surface, condensation polymerisation started and proceeded rapidly owing to the enhanced heat and mass transfer achieved due to the thin films and high shear mixing provided by the grooves on the disc. The ease with which water vapour was removed from the reaction system determined the rate of polymerisation. The reactions were carried out in a closed system under a blanket of nitrogen at 1 atm to prevent oxidation and other side reactions. The viscous polymer melt was thrown off the heated disc surface on to the water cooled trough to prevent degradation of the polymer. Samples were collected after every run and prepared for analysis.

Analysis of samples

Acid value or molecular weight analysis was performed as a measure of conversion in the condensation polymerisation runs.

The acid value is a measure of the amount of free acid groups in the polymer melt and is expressed in terms of the number of milligrams of potassium hydroxide required to neutralise 1 g of sample using a phenolphthalein indicator, or in mathematical terms:

$$\mathrm{AV} = \frac{56.1\,VN}{W} \qquad (17)$$

where AV = Acid value (mg KOH/g of polymer), V = volume of potassium hydroxide used for titration (ml), N = normality of potassium hydroxide solution (mol dm^{-3}) and W = weight of test sample (g).

Typically, the mass of a sample used for determining the acid value is *ca.* 1.5 g and is accurately measured to ±0.001 g. The titre of 0.1 N KOH is typically 15 ±0.1 ml.

Thus, the accuracy of the acid number calculation will be:

$$\mathrm{AV} = \pm\left[\frac{100\times 0.001}{1.5} + \frac{100\times 0.1}{15}\right]\%$$
$$\mathrm{AV} = \pm 0.7\%$$

Samples from the SDR runs using the supplied unsaturated polyester prepolymer (reaction II) were analysed for molecular weights and molecular weight distributions (MWD) using GPC.

Results and discussion

Unsaturated polyesterification: reaction I

Results of the tests which were carried out to study the change in the acid value (AV) of the unsaturated polymer ester melt from reaction I as it proceeds from the prepolymer stage to the final stage are presented in Table 1 which also shows the savings in time that were achieved by using the spinning disc polymeriser by bench marking the performance of the spinning disc polymeriser with that of a conventional batch reactor. Figs. 7 and 8 which benchmark the performance of the spinning disc polymeriser suggest that it is suitable for reaction systems when the acid value has dropped to below 300, *i.e.* when the melt is viscous.

When the acid value is > 300, the reaction is fast and is not mass transfer limited. Even though there is a significant drop in the acid number when the spinning disc is used, there is very little reduction in the reaction times when compared with a conventional batch reactor. The reaction is fast in this region of the profile, and so the use of the disc does not have any

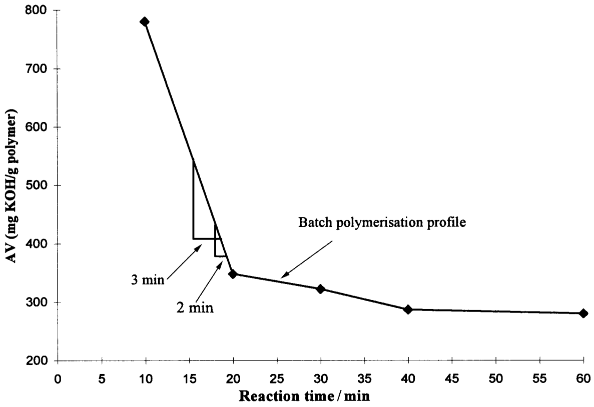

Fig. 7 Time saving in spinning disc reactor for AV > 300.

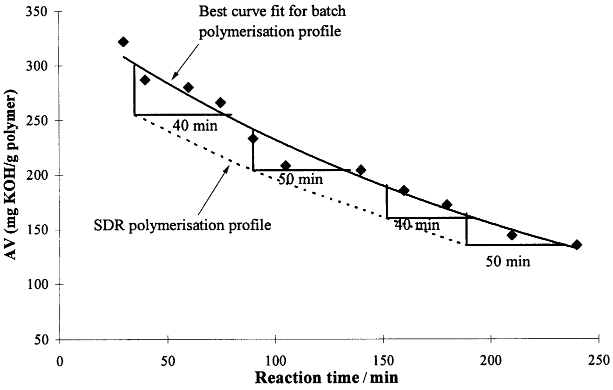

Fig. 8 Time saving in SDR for AV < 300.

Table 1 Changes in acid value in the SDR for unsaturated polyester (reaction I)

Initial acid value (SDR feed)/ mg KOH g^{-1}	Final acid value (SDR Product)[a]/ mg KOH g^{-1}	Disc temperature/°C	Disc speed/rpm	Equivalent batch time min (Saving in time by using SDR)
547 ± 16	408 ± 12	200	1000	3
428 ± 13	378 ± 11	200	1000	2
300 ± 9	255 ± 8	200	1250	40
233 ± 7	204 ± 6	200	1000	50
190 ± 6	160 ± 5	200	1000	40
164 ± 5	136 ± 4	200	1000	50

[a] Acid number values include the ±3% uncertainty.

significant impact on the reaction rate. The spinning disc increases the mass and heat transfer in the melt, but in the initial stages, the reaction is not mass transfer controlled, and so the disc does not give significant increases in the rate of reaction. Therefore, the spinning disc will not be of use industrially for the initial stages of the polymerisation reaction. A further increase in the conversion in the region of high acid values and hence a further increase in the time saving over the disc could be achieved by increasing the residence time of the melt on the disc. At these high acid values, the melt has a relatively low viscosity, and so has a low residence time on the disc; it is quickly thrown off. Increasing the residence time could be achieved by reducing the disc rotational speed, but this is not efficient. It is simpler and more efficient to perform this fast initial stage of the reaction in the prepolymer stage, and save the disc, which uses more energy to operate, for the higher viscosity melt.

When the acid value is < 300 the spinning disc polymeriser seems to perform much better than the batch reactor. As seen from Fig. 8, for acid values < 300 *ca.* 50 min is saved every time the melt was treated on the spinning disc (*i.e.* one pass through the spinning disc polymeriser). The batch process in this range of acid value is very slow owing to the high viscosity of the melt. The rate of reaction is then controlled by the rate of mass transfer. The spinning disc, as expected, increases the rate of reaction and therefore there is a significant reduction in the reaction time. Increasing the residence time of the melt on the disc could increase the conversion further. Decreasing the rotational speed of the disc could do this, as well as decreasing the force exerted on the melt. However, this would increase the film thickness on the disc, and so decrease the mass transfer in the melt. This would in turn decrease the rate of reaction, which is mass transfer controlled, and so the overall conversion would not increase significantly, if at all. An optimum rotational speed is required, which must be determined experimentally. A better method of increasing the residence time of the melt on the disc would be to increase the disc diameter which would lead to the melt taking longer to flow over the disc, and so increase the reaction time, and also the ‘extra’ part of the disc would have an even thinner film, owing to the increase in circumference as the fluid flows outwards. An optimum disc diameter is required, balancing up this increase in reaction rate with the increasingly complex mechanical design of the large diameter disc and the increase in energy to rotate it. Therefore, the spinning disc could have applications in industry with higher viscosity melts. This fits in with the initial concept of the spinning disc as a polymer reactor.

Unsaturated polyesterification: reaction II

The molecular weight changes in the SDR for the tests with the prepolymer from reaction II at various disc operating conditions are shown in Table 2.

The effects of the various operating conditions in the SDR on the change in M_w are seen in Figs. 9 and 10.

From Fig. 9, it is observed that, for the prepolymer feed with a low initial M_w of 600, a rise in disc temperature gives a progressively higher molecular weight change until a maximum temperature of *ca.* 270 °C. For the prepolymer with initial M_w of 2600, the change in M_w is much greater than for the low molecular weight prepolymer at 210 °C. However, a further rise in temperature causes the molecular weight to drop by *ca.* 160, indicating that degradation of the polymer has occurred on the disc. Temperature affects the two prepolymers in very different ways and this may be attributed to their widely different residence times as a result of viscosity differences. Hence, the prepolymer with high M_w of 2600 would be more viscous and therefore takes more time to flow across the disc surface at a given rotational speed than the low molecular weight pre-

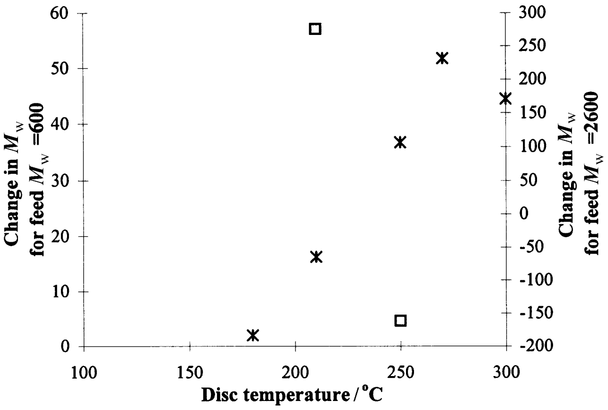

Fig. 9 Effect of disc temperature on change in M_w at a fixed disc rotational speed of 200 rpm. ⚹ = feed M_w = 600; ☐ = feed M_w = 2600.

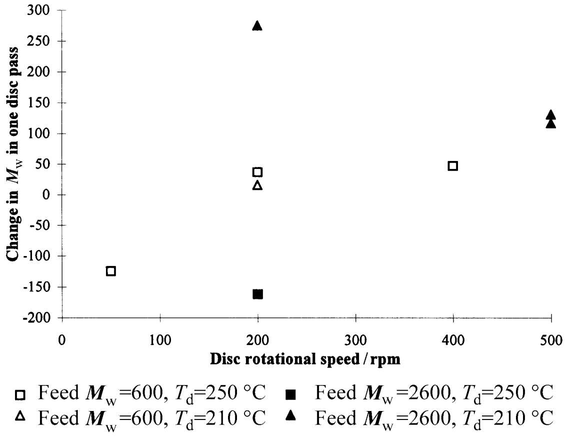

Fig. 10 Effect of disc speed on molecular weight changes in SDR at different disc temperatures T_d for different SDR feed M_w.

Table 2 Changes in M_w in the SDR for unsaturated polyester prepolymer (reaction II)

SDR feed temperature/°C	SDR feed M_w	SDR product M_w (average)	Change in M_w (average)	Disc temperature/°C	Disc speed rpm
37	554	556	2	180	200
35	554	591	37	250	200
34	552	599	47	250	400
33.5	558	610	52	270	200
32	558	603	45	300	200
34.6	541	417	−125	250	50
34	554	570	16	210	200
52.4	2568	2406	−162	250	200
52.2	2628	2903	275	210	200
51	2791	2923	132	210	500
51.1	2274	2391	117	210	500

polymer. It would consequently be more sensitive to temperature increases with a tendency to degrade more rapidly at higher temperatures than the low molecular weight polymer.

Fig. 10 shows the effect of disc rotational speed on the average change in molecular weight in one disc pass for both the low and high molecular weight feeds at various disc temperatures. Considering the feed with M_w of 600 fed onto the disc maintained at 250 °C, it is seen that at the low speed of 50 rpm, degradation of the polymer occurs, as indicated by the reduction in molecular weight of the disc product. This is probably caused by the excessively long residence times on the disc surface. As the rotational speed is increased, the molecular weight of the product rises by 37 at 200 rpm and by 47 at 400 rpm. A more significant improvement was obtained in the results for the prepolymer with initial M_w of 2600. With a disc temperature of 210 °C and a disc speed of 200 rpm, the increase in the molecular weight was *ca.* 275 dropping to about half this value at the higher speed of 500 rpm. However, with the disc at a temperature of 250 °C, a decrease in molecular weight of *ca.* 160 showed that degradation had occurred at that temperature. Therefore, the optimum operating conditions for the high molecular weight feed seem to be a disc temperature of 210 °C and speed of 200 rpm.

The molecular weight distribution was assessed by measuring the polydispersity index (PDI) of the polymer sample which is given as the ratio $\overline{M}_w/\overline{M}_n$. The PDI for the low molecular weight feed (M_w = 600) was in the range 1.2–1.3 and that for the high molecular weight feed (M_w = 2600) was *ca.* 3.5–4.5. For all the runs on the spinning disc, the maximum increase in the polydispersity index of the product polymer was no more than 0.2 compared to the feed polymer regardless of the feed molecular weight.

It can be concluded that the higher molecular weight and hence higher viscosity feed gives the larger increase in molecular weight in one disc pass under the same disc operating conditions in comparison to the low molecular weight feed. It has also been demonstrated that it is important to select an appropriate operating temperature which is high enough for rapid polymerisation but low enough to prevent any degradation to occur. For the conditions tested, it was found that the optimum operating conditions for the highly viscous prepolymer (M_w = 2600) were a temperature of 210 °C and a disc speed of 200 rpm while for the prepolymer with M_w of 620, a temperature of 270 °C and a disc speed of 200 rpm gave the largest change in molecular weight. Furthermore, the polydispersity index of the SDR polymer changed little in comparison with the feed polymer indicating that significant progress in polymerisation could be achieved in the SDR whilst maintaining reasonably tight molecular weight distributions.

Saturated polyesterification: reaction III

The results of the spinning disc runs for the saturated polyesterification process (reaction III) are presented in Figs. 11–15 for four different feeding or prepolymerisation times ranging from 1 to 4 h. The batch calibration profile is shown in its entirety over 4 h of polymerisation time in Fig. 11.

Figs. 12–15 represent magnified sections of the batch calibration curve in the regions of interest where spinning disc data have also been plotted by way of comparison to the batch polymerisation.

The performance of the SDR is measured in terms of savings in reaction time assuming a residence time of the order of on the disc. The dotted lines in Figs. 12–15 represent portions of the batch calibration curve which have been shifted in order to compensate for the differences in acid values between the actual feed and the calibrated value. Such a difference is a direct result of the fluctuations in batch exotherm which was difficult to control accurately.

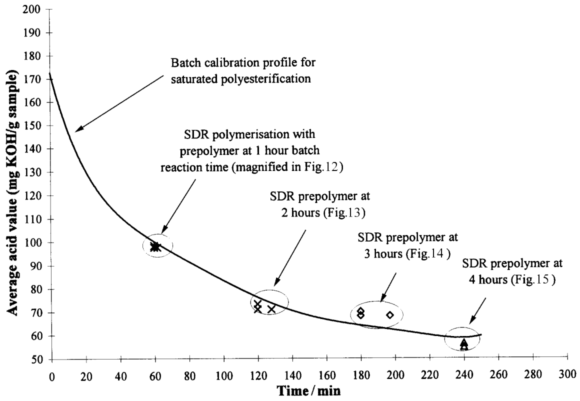

Fig. 11 Batch calibration profile showing regions which have been compared with spinning disc reactor performance (magnified portions shown on separate graphs as indicated).

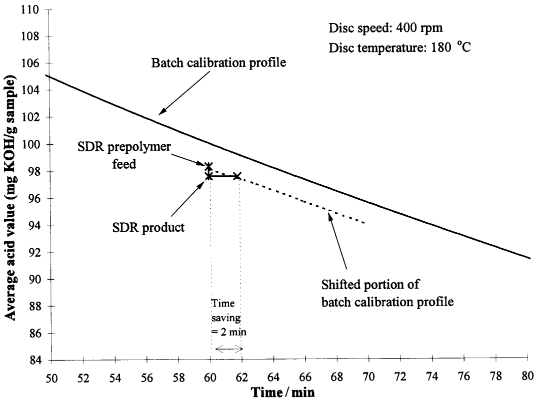

Fig. 12 SDR performance at 1 h prepolymerisation time.

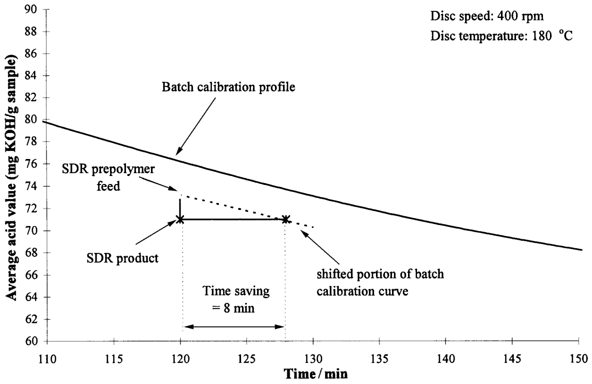

Fig. 13 SDR performance at 2 h prepolymerisation time.

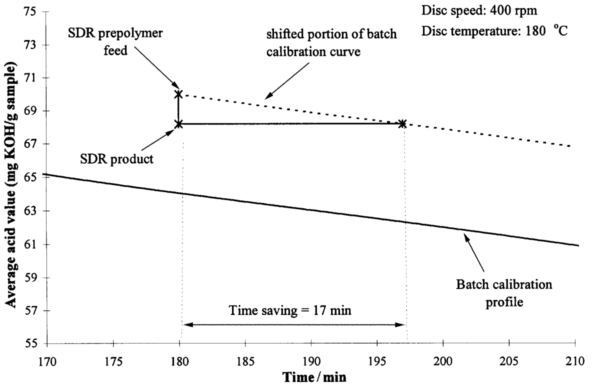

Fig. 14 SDR performance at 3 h prepolymerisation time.

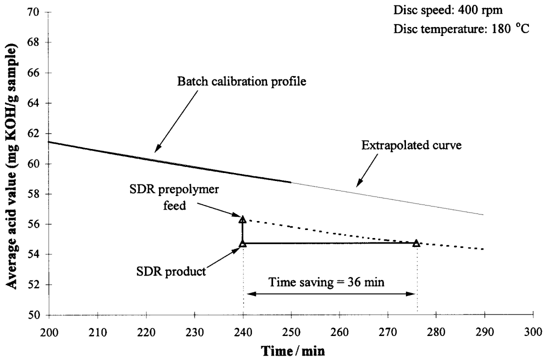

Fig. 15 SDR performance at 4 h prepolymerisation time.

All of the SDR time saving results have been condensed in Fig. 16 which shows the rapid increase in reaction time saving with prepolymerisation time. This clearly indicates that the spinning disc performs better as the viscosity of the prepolymer builds up. At high viscosities, it appears that the diffusion control limitations imposed by the bulk viscous reaction mixture in the batch reactor system are easily overcome in the thin film formed on the rotating disc surface enabling the polymerisation to proceed in the SDR at its inherently faster rate.

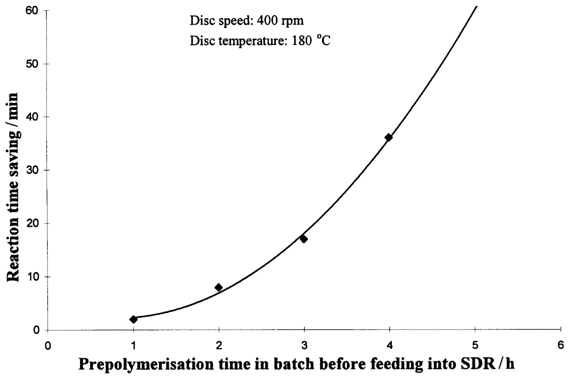

Fig. 16 Saving in reaction time using the spinning disc reactor for different prepolymer feeds.

Conclusions

From the present study it may be concluded that a spinning disc reactor has the potential to be used as a polymeriser owing to its enhanced transport rates. Significant reductions in the reaction times and tight control of the molecular weight distribution of the polymer have been achieved in one pass in a spinning disc polymeriser. It could be feasible to perform the entire polycondensation process in a spinning disc reactor using neat monomer as the starting material to obtain high molecular weight end-product. This may be possible if the reaction is performed at higher temperatures of *ca.* 400 °C to give even faster rates of polymerisation as had been suggested by tests performed on thin static films at high temperatures in an earlier study.[4] Temperature is seen to be a significant parameter in the enhancement of the speed of polymerisation.[4,5] Unfortunately we could not perform tests at temperatures above 300 °C as the existing test facility was not designed for use at high temperatures. Another alternative is to increase the residence time in the SDR from 2–3 s to possibly 1 min. This may be possible by using a thermally conductive mesh system which has been shown to significantly increase the residence time. Alternatively a rotating packed bed may be used.

However a more practical approach would be to perform the initial stages of the polymerisation in a twin screw extruder with venting facility and perform the difficult part of the polymerisation in a spinning disc reactor. For such a system a residence time of 10–15 s may be required in the SDR and a meshed disc 500 mm in diameter will be adequate in providing a throughput of 1 tonne h^{-1}. We envisage that a single shaft may be able to house three discs and therefore one single rotating system may be capable of delivering approximately three tonnes h^{-1} of polymer.

A process based on the SDR technology will significantly reduce the footprint, improve the inherent safety as well as improve the energy efficiency of the plant. The SDR appears to have the potential of producing high conversion polymers with tight molecular weight distribution and hence better product quality which would significantly improve the prospects of the technology. One area in which it is believed more work needs to be done concerns process monitoring and control of fast response processes. As the melt will have very short residence time the control strategies may be based on feed forward techniques.

Finally a spinning disc polymeriser could significantly improve the intrinsic safety of the polymerisation process. However before any major conclusions can be drawn, detailed studies have to be carried out to understand the effect of system variables such as disc temperature, disc diameter and the prepolymer flow rate on the polymerisation process.

Appendix

Flow on a horizontal smooth disc rotating about a vertical axis (Fig. 17) is more appropriately represented by considering vertical cylindrical coordinates (r, θ, z).

The modified Navier–Stokes equation is then given by the following expressions: In the radial direction, r

$$\rho\frac{Dv_r}{Dt}-\rho\frac{v_\theta^2}{r}=\mu\left(\nabla^2 v_r-\frac{v_r}{r^2}-\frac{2\partial v_\theta}{r^2\partial\theta}\right)-\frac{\partial p}{\partial r}+\rho g_r \quad \text{(A1)}$$

In the angular direction, θ:

$$\rho\frac{Dv_\theta}{Dt}-\rho\frac{v_\theta v_r}{r}=\mu\left(\nabla^2 v_\theta-\frac{v_\theta}{r^2}+\frac{2}{r^2}\frac{\partial v_r}{\partial\theta}\right)-\frac{1}{r}\frac{\partial p}{\partial\theta}+\rho g_\theta \quad \text{(A2)}$$

In the vertical z direction:

$$\rho\frac{Dv_z}{Dt}=\mu\nabla^2 v_2-\frac{\partial p}{\partial z}-\rho g_z \quad \text{(A3)}$$

where

$$\frac{D}{Dt}=\frac{\partial}{\partial t}+v_r\frac{\partial}{\partial r}+v_\theta\frac{\partial}{\partial\theta}+v_z\frac{\partial}{\partial z}$$

$$\nabla^2=\frac{\partial^2}{\partial r^2}+\frac{1}{r}\frac{\partial}{\partial r}+\frac{1}{r^2}\frac{\partial^2}{\partial\theta^2}+\frac{\partial^2}{\partial z^2}$$

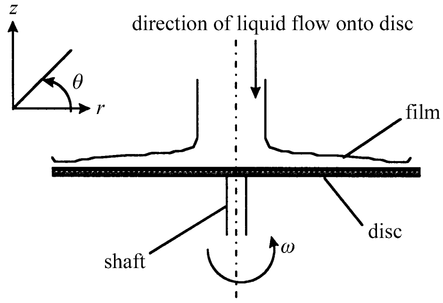

Fig. 17 Thin film flow on a rotating disc.

The equation governing the conservation of mass also termed the continuity equation must also be satisfied for the flow system and it is given by:

$$\frac{\partial \rho}{\partial t} + \nabla(\rho v) = 0 \qquad \text{(A4)}$$

Eqn. (A4) can be expressed for the horizontal rotating disc system as:[23]

$$\frac{\partial \rho}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(\rho r v_r) + \frac{1}{r}\frac{\partial}{\partial \theta}(\rho v_\theta) + \frac{\partial}{\partial z}(\rho v_z) = 0 \qquad \text{(A5)}$$

Considering an incompressible fluid where the density ρ is constant, eqn. (A5) can be further simplified to give:

$$\frac{1}{r}\frac{\partial}{\partial r}(r v_r) + \frac{1}{r}\frac{\partial v_\theta}{\partial \theta} + \frac{\partial v_z}{\partial z} = 0 \qquad \text{(A6)}$$

or, on expansion,

$$\frac{\partial v_r}{\partial r} + \frac{v_r}{r} + \frac{1 \partial v_\theta}{\partial \theta} + \frac{\partial v_z}{\partial z} = 0 \qquad \text{(A7)}$$

Therefore, fluid flow in a rotating system is fully defined by eqns. (A1), (A2), (A3) and (A7).

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Solvent-free synthesis of 3-carboxycoumarins†

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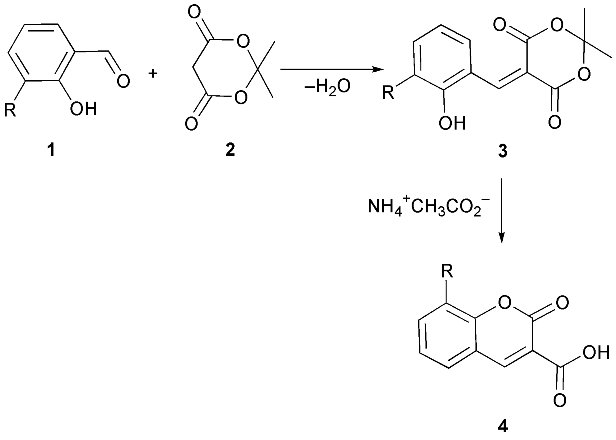
3-Carboxycoumarins, an important class of biologically active compounds, are synthesized in very high yield and in an energy efficient manner, without use of noxious reagents or volatile organic solvents, either by direct reaction of the solid reagents, or in an aqueous slurry. Remarkably, even though the first step in the reaction cascade is a condensation reaction, the reaction proceeds rapidly as a stirred aqueous slurry without application of heat. A reason for this phenomenon is advanced and recycling of the aqueous filtrate post product separation is described. Although the reaction is not 100% atom efficient (1 mole of acetone is evolved for each mole of coumarin produced) it is a significant improvement on previously described methods for the synthesis of such compounds.

Introduction

The 1-benzopyran-2-one, or coumarin, subunit appears in a vast range of natural products and, due to the high levels of biological activity exhibited by many such compounds, has been duplicated in numerous synthetic compounds exhibiting pharmaceutical activity. The reaction of active methylene compounds with 2-hydroxybenzaldehydes, an example of the Knoevenagel reaction, has been extensively used as the first step in the synthesis of 3-carboxycoumarins and Knoevenagel himself described the solution phase condensation of 2-hydroxybenzaldehydes with malonic acid more than 100 years ago.[1] Numerous synthetic routes to 3-substituted coumarins from 2-hydroxyarylaldehydes or 2-hydroxyarylketones have been published including syntheses requiring the use of noxious phosphorylating agents such as $POCl_3$,[2,3] bases such as piperidine[4] or solvents such as DMF.[5] Recently a 'solid phase' synthesis of substituted 3-carboxycoumarins utilising ethyl malonate tethered to a Wang resin and suspended in pyridine has been described,[6] although reported yields are poor and often significantly less than 50%.

Analysis of the numerous routes to coumarins such as **4** (see Scheme 1) shows that simple, efficient 'green' methodology to this important class of heterocyclic compounds is lacking. Bandgar *et al.* have recently published a one-pot, microwave-mediated synthesis of substituted 3-carboxycoumarins which entails the use of solid catalysts.[7] While this method circumvents the use of noxious acids, bases or solvents it is not solvent-free as the product must be removed from the catalyst by dissolution in a volatile organic solvent and product purification by column chromatography is deemed necessary.



Scheme 1 **a** R = OMe, **b** R = H.

Results and discussion

We now report the facile synthesis of 3-carboxycoumarins from 2-hydroxybenzaldehydes and Meldrum's acid by a room-temperature solid/solid or solid/liquid reaction with catalytic amounts of ammonium acetate. Quantitative conversion of starting materials is readily achieved without heating and no volatile organic solvents are required, with product purification achieved by an aqueous wash yielding an aqueous solution containing ammonium acetate which may be reused in subsequent reactions. Toda has reported numerous solid/solid reactions[8] and we have recently described solvent-free syntheses of Aldol condensation products[9] and cyclic bowl shaped compounds.[10] The facility with which condensation reactions proceed under these conditions led us to attempt the synthesis of 3-carboxycoumarins in ground mixtures of neat reagents with remarkable results.

Grinding of solid *o*-vanillin **1a** with solid Meldrum's acid **2** leads to the almost quantitative formation of the Knoevenagel

Green Context

The development of solvent-free reactions is an important step towards simplifying reaction systems and minimising waste. However, most such systems described in the literature require the use of solvents during the isolation stage, thus making the *process* as a whole solvent-intensive. Here, a solid state (or aqueous slurry) route to coumarins has been developed, which uses a water-soluble catalyst. Reaction takes place readily and efficiently, and the isolation is simply a filtration after suspension in water to remove the catalyst. ***DJM***

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† Electronic supplementary information (ESI) available: cell dimensions *vs.* temperature of data collection for **4a**. See http://www.rsc.org/suppdata/gc/b0/b006704k/

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product **3a** while addition of catalytic amounts of ammonium acetate to the mixture of solid reagents results in almost quantitative conversion to **4a** (Scheme 1). Isolation of the product is achieved by slurrying in water followed by filtration and drying.‡ The bright yellow intermediate benzylidine Knoevenagel product **3a** may be isolated from reaction mixtures containing no ammonium acetate. A similar reaction with liquid salicylaldehyde **1b** and Meldrum's acid in the presence of ammonium acetate yields the corresponding coumarin **4b** quantitatively. Grinding of liquid **1b** and solid **2** without catalyst does not, however, lead to significant formation of **3b**.

The unequivocal identification of solid products obtained in solid/solid reactions requires the use of non-solution analytical or spectroscopic methods and to this end molecular structure and geometry of each of the products, **3a**, **4a** and **4b** has been established by single crystal X-ray diffractometry.§ The molecular structures of **3a** and **4a** are illustrated in Fig. 1 and X-ray powder diffraction patterns obtained from solid samples of reaction products were compared with those generated from single crystal data[11] to verify that the reaction had indeed occurred in the solid or slurry forms and the products were not an artifact of analysis. Fig. 2 illustrates the comparison between the powder pattern generated from single crystal data and solid/solid and slurry reaction products for compound **4a**.¶

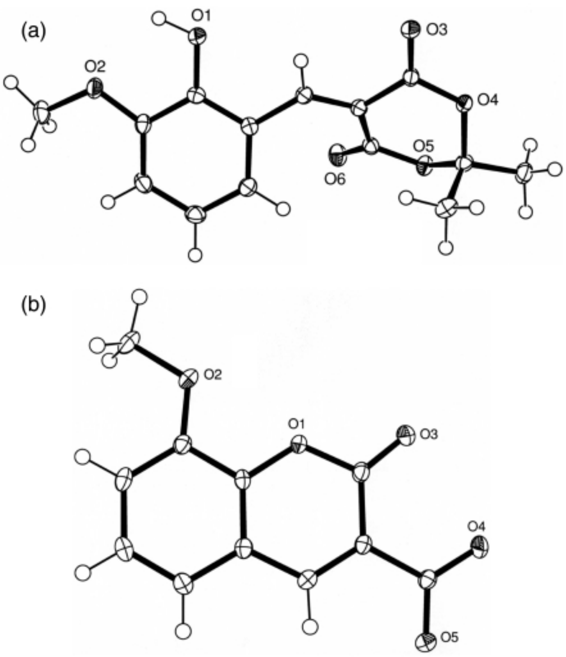

Fig. 1 ORTEP molecular diagrams, with ellipsoids at 50% probability, of (a) benzylidine intermediate **3a** and (b) coumarin product **4a**. The preferred *E*-configuration of the intermediate in the solid state is clear.

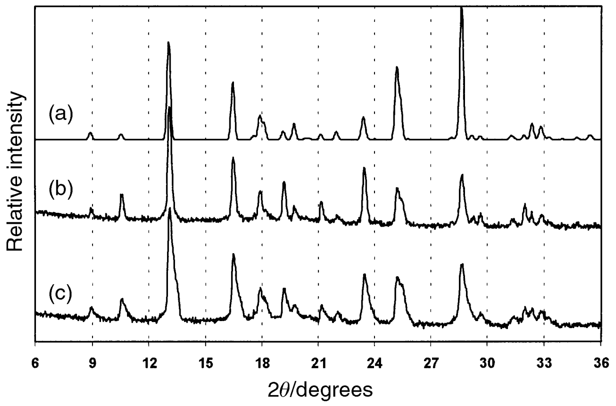

Fig. 2 Comparison between X-ray powder diffraction patterns of coumarin products **4a** produced by solid grinding method (c), aqueous slurry method (b) and the calculated pattern derived from single crystal data (a) and corrected for room-temperature cell dimensions.

Remarkably, in spite of the extremely low aqueous solubility of both Meldrum's acid and the benzaldehyde derivatives used, the reaction may be carried out in an aqueous solution of ammonium acetate, yielding 3-carboxycoumarins of high purity in almost quantitative yield. The aqueous ammonium acetate solution obtained once the solid product is filtered off may be reused in further reactions without detriment to product quality. Alternately the benzylidine intermediate **3a** may be isolated from a reaction mixture containing no catalysts and slurried in aqueous ammonium acetate to yield the same result. The reaction proceeds most rapidly when powdered reagents are added directly to a stirred aqueous solution of ammonium acetate. This holds true even in the reaction with salicylaldehyde **1b** (a viscous liquid) where a separate organic phase is formed upon addition to aqueous ammonium acetate. As the reaction proceeds this oily phase is consumed and a white slurry results.

It is generally accepted that the second step in the Knoevenagel reaction, the 1,2-elimination, is inhibited in protic solvents[12] and this may provide a clue to the increased rate of reaction in aqueous slurry. The benzylidine formed crystallises as the *E*-isomer yet only the *Z*-isomer has the correct orientation for ring closure to the coumarin. If 1,2-elimination is inhibited and hydrolysis of Meldrum's acid and ring closure proceeds once the β-hydroxydiketone is formed, *i.e.* before or concomitantly with 1,2-elimination of water, then, the longer lived the flexible β-hydroxydiketone, the more favourable the conditions for coumarin formation and the more rapid the reaction.

We have demonstrated a convenient, clean and efficient method for the formation of an important class of biologically active compounds that obviates the need for polar aprotic solvents such as DMF or solid acid catalysts and requires no organic solvent or heat. The product is of high purity and waste is minimised.

Experimental

^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer in $CDCl_3$ or d_6-acetone solution with TMS as reference.

Crystals suitable for single crystal diffractometry were prepared from isolated products by deposition from acetone or acetone–dichloromethane solutions. Data for all structures were collected on an Enraf-Nonius Kappa CCD at 123 K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, 1° φ and ω scans). Structures were solved by direct methods using the program SHELXS-97[13] and refined by full matrix least squares refinement on F^2 using the programs SHELXL-97[14] and Xseed.[15] Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted at geometrically determined positions with temperature factors fixed at 1.2 times that of the parent atom except for methyl hydrogen atoms where the temperature factors were constrained to equal 1.5 times that of the parent carbon atom.

Solvent free reactions

Powdered reagents (1 : 1 molar ratio) were gently ground together in a mortar and pestle and a catalytic amount of $NH_4^+MeCO_2^-$ (0.05–0.15 mol equivalents based on the benzaldehyde derivative) added and the reagents thoroughly mixed by grinding. The resultant sticky mass was allowed to stand, with occasional grinding, overnight or until no starting material was detectable by TLC analysis. The ground mixture underwent a series of colour and consistency changes from white powders to sticky bright yellow material to off-white or beige solid. After regrinding, the product was suspended in water to dissolve the catalysts, filtered off, washed with water and dried in air.

Slurry reactions

Powdered reagents (1 : 1 molar ratio) were stirred in water (*ca.* 10 volumes based on reagent mass) to produce a slurry. A catalytic amount of $NH_4^+MeCO_2^-$ (0.05–0.15 mol equivalents based on the benzaldehyde derivative) was added and the slurry stirred overnight. The resultant white or beige slurry was filtered and the product dried in air. The filtrate was retained for reuse in further reactions.

Acknowledgements

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Notes and references

‡ ^{1}H NMR spectra of coumarins prepared by both slurry and solid/solid methods indicate products of high purity, while **3a** shows traces of coumarin.

§ *Crystal data*: for **3a**: $C_{14}H_{14}O_6$, M_r = 278.25, triclinic, space group $P\bar{1}$, a = 5.9637(2), b = 9.1230(6), c = 12.0646(7) Å, α = 99.666(3), β = 96.329(3), γ = 95.837(3)°, V = 638.28(6) Å^3 , Z = 2, μ(Mo-Kα) = 0.114 mm^{-1}. Of 5454 reflections measured, 2985 were unique with 2221 having $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] R_1 = 0.0437, wR_2 = 0.0673, GOF on F^2 = 1.037 for 188 refined parameters and one restraint (OH bond length).

For **4a**: $C_{11}H_8O_5$, M_r = 220.17, monoclinic, space group $P2_1/c$, a = 5.1100(2), b = 19.5292(4), c = 9.4299(3) Å, β = 99.909(2)°, V = 927.01(5) Å^3, Z = 4, μ(Mo-Kα) = 0.127 mm^{-1}. Of 4155 reflections measured, 2151 were unique with 1583 having $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$] R_1 = 0.0437, wR_2 = 0.0690, GOF on F^2 = 1.037 for 146 refined parameters and zero restraints. The carboxylic acid group is disordered with apparent C–O bond lengths intermediate between expected single and double bond lengths and the largest residual electron density peaks were found at 0.8–0.9 Å from the oxygen atoms suggesting two carboxylic H positions. The carboxylic H-atoms were not included in the model.

For **4b**: colourless, tabular crystals were found to have cell dimensions indistinguishable from those found by Dobson and Gerkin.[16]

CCDC 1048/3. See http://www.rsc.org/suppdata/gc/b0/b006704k/ for crystallographic files in .cif format.

¶ Single crystal data was collected at 123 K while powder data was collected at 294 K. Measurements of cell dimensions at temperatures between 123 and 293 K indicate distinct anisotropic shrinkage of cell dimensions (ESI†) which are corrected for in the calculated powder pattern.

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On oxyhalogenation, acids, and non-mimics of bromoperoxidase enzymes

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In contrast to recent studies, molybdenum(VI) and vanadium(V) catalysed oxidative bromination reactions are found to depend on the presence of stoichiometric amounts of acid. Thus, recent reports on Lewis-acid catalysed oxybromination systems are re-examined. The relevance of these systems as bromoperoxidase enzyme mimics and also the potential application of enzymatic halogenation as a 'green' bromination option are discussed.

Introduction

The elimination of chlorine- and bromine-containing organic compounds (VOCs and PBBs/PCBs) has been targeted by recent legislation.[1] While the growing number of halometabolites identified in recent years questions the validity of campaigns for total elimination of halogenated organics from our environment,[1d] it is certain that many existing halogenation processes do not advance the goal of non-toxic, waste-free chemistry.[2] A case in point is the bromination of aromatic compounds [eqn. (1)], which utilizes only 50% of the available

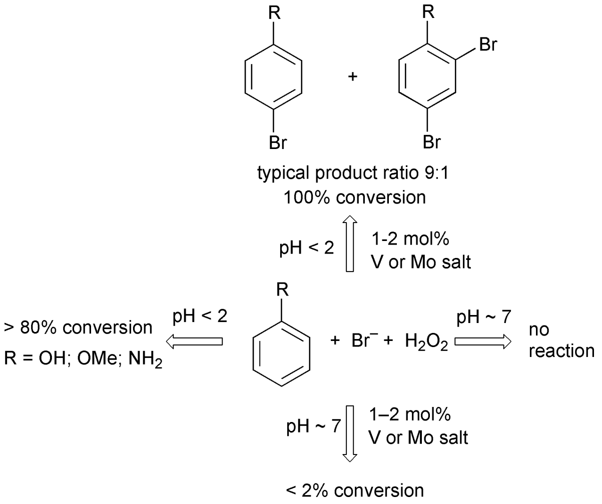
$$\mathrm{ArH + Br_2 \longrightarrow ArBr + HBr} \qquad (1)$$

halogen, with the other half forming HBr waste. For deactivated compounds, this reaction requires also stoichiometric amounts of Lewis acids (*e.g.* $AlCl_3$), increasing the volumes of waste streams. Further complications can arise from transportation/storage of large quantities of molecular bromine or HBr. These reasons enhance the appeal of bromination protocols based on bromide salt oxidation with hydrogen peroxide, often envisaged in a manner similar to the biohalogenation performed by haloperoxidase enzymes. In fact, several recent reports claim oxidative bromination to be *the* solution to replace all eco-deficient bromination reactions.[3–8] To quote one example: 'Consequently, what is needed is a methodology that would be environmentally friendly and clean and yet efficient, site-selective, operationally simple, and cost-effective'. Obviously, it is much safer and cheaper to transport and store large quantities of bromide salts than either Br_2 or HBr, but the drawback of the bromide salt oxidation process is that it depends on *acidic* conditions, so that the reaction $H_2O_2 + 2Br^- \rightarrow 2BrO^- + 2OH^-$, produces only small amounts of hypobromite.

Here we re-examine some oxybromination protocols (all published in the 1990s) in the light of new experimental data, and discuss the relevance of these reagent systems as bromoperoxidase enzyme mimics, and also the utilisation of haloperoxidase systems for large-scale bromination.

Results and interpretation

As part of our study on the development of eco-efficient oxyhalogenation processes, we examined various V and Mo salts as potential oxybromination catalysts. We found (Scheme 1) that neither activated aromatics (phenol, aniline, anisole) nor non-activated ones (benzene, toluene) reacted with MBr (M = Na, K) in the presence of molar equivalents of hydrogen peroxide at 5 < pH < 7 (no reaction refers to < 1% substrate conversion). Moreover, even with catalytic amounts (1–2 mol%) of V_2O_5, NH_4VO_3, or ammonium molybdate, < 2% substrate conversion was observed. Conversely, reactions proceeded to completion (provided that 1.5–2.5 excess equivalents of hydrogen peroxide were added, owing to some unproductive peroxide decomposition) when the medium was acidified to 1 < pH < 2, using either H_2SO_4, HCl, HNO_3, H_3PO_4 or AcOH. It should be noted that when olefins, phenols



Scheme 1 Oxidative bromination of aromatics. *Reagents and conditions*: 10 mmol substrate, 20 mmol bromide (KBr or NaBr), 25 mmol H_2O_2; 10 g H_2O; 700 rpm stirring; 25 °C; R = OH; OMe; NH_2; Me; Et.

Green Context

The efficient use of bromine in bromination reactions is an ongoing area of research, with the majority of processes allowing for only 50% atom economy, and an equivalent of HBr being produced. This paper discusses recent attempts to circumvent this problem, and casts some light on the possibilities and pitfalls of various approaches. The key requirement for successful oxybromination appears to be the activation of the oxybrominated species without the use of stoichiometric quantities of acid. ***DJM***

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or anilines were used as substrates, over 80% conversion was measured under these acidic conditions also in the absence of the metal catalyst. As these results are not in complete agreement with published reports, a comparison is in order.

A promising study claimed that 75–85% of *p*-bromoacetanilide could be isolated using hydrogen peroxide, catalytic V_2O_5, acetanilide and KBr.[3] When unable to reproduce those results, we contacted the author, who acknowledged that stoichiometric V_2O_5 was used. In a later report,[4a] stoichiometric NH_4VO_3 was observed to catalyse [*sic*] the oxybromination of olefins and phenolic ethers. More recently, similar 'catalysis' was reported when semi-stoichiometric (50 mol% of catalyst) Na_2MoO_4 or NH_4VO_3 was reacted with KBr, hydrogen peroxide and olefins (at $pH < 1$).[4b] The need to use stoichiometric amounts of these salts stems from the necessity for an acidic medium for the bromide oxidation reaction. This was given some attention in another publication, which reported the oxybromination of naphthols with 10 mol% NH_4VO_3, hydrogen peroxide and KBr. Analogous oxychlorination was observed using KCl, but (expectedly) no reaction occurred with KF.[5]

In further examples, 'hazardous' bromine was replaced by 48% HBr, hydrogen peroxide, and 10 mol% sodium tungstate (all in glacial acetic acid) for the oxybromination of phenyl methyl ethers[6a] and anilines.[6b] Analogous studies have been carried out on oxyiodination.[6c] Similarly, a solution of KBr in glacial acetic acid has been substituted for 'highly toxic' aqueous HBr.[7] Last, but not least, an 'environmentally favorable synthetic protocol' was reported in which 'regioselective bromination of organic substrates by tetrabutylammonium bromide promoted by V_2O_5–H_2O_2' was described as an efficient, straightforward and cheap alternative to classical bromination reactions.[8] However, it is questionable if this process is environmentally favourable or efficient since stoichiometric amounts of V_2O_5, TBAB and an excess of H_2O_2 were used. It is certainly not cost-effective, as discussed herewith.

Discussion

Chemical aspects of metal-catalysed oxyhalogenations using hydrogen peroxide

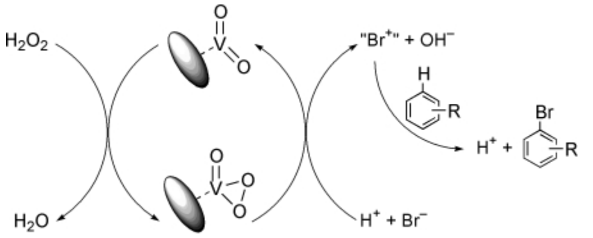
The kinetics and the thermodynamics of the reactions between H_2O_2 and the halides (including hydrogen halides) in aqueous solution have been extensively studied.[9] Vanadium and molybdenum both react readily with aqueous hydrogen peroxide, forming, as was shown previously in the case of vanadium,[10] various oxo- and peroxo-complexes. These in turn can facilitate the transfer of an oxygen atom to Br^- in a two-electron redox process. However, the problem that manifests itself in the application of oxidative bromination is not the formation of a 'positive bromine' species (this can be accomplished simply by adding H_2O_2 to Br^- at low pH[11]). Rather, it is the low reactivity of this brominating species under the acidic, aqueous conditions.[12] It is no coincidence that in all of the examples given above the so-called 'efficient' oxybromination was demonstrated on anisoles, phenols, anilines and their derivatives. All these substrates are super-reactive towards electrophilic substitution. Moreover, examples using alkenes and alkynes as substrates are irrelevant from the green chemistry viewpoint, as the addition of molecular bromine to unsaturated carbon–carbon bonds is not only more facile than oxybromination, but in most cases waste-free. Although studying model substrates is a customary practice in organic chemistry, in this case, more often than not the model system is inapplicable to most classes of compounds (*i.e.*, those that are not phenols or anilines). In fact in 1987, Dakka and Sasson pointed out that except for these most activated substrates, the presence of a Lewis acid catalyst was mandatory for aromatic oxyhalogenation, and demonstrated the utility of quaternary ammonium salts in such reactions.[13] The development of cheap, water- and acid-stable Lewis acid catalysts remains a challenge to green chemists.

Cost-effectiveness and environmental aspects of oxybromination processes

Molecular bromine carries significant industrial advantages, including low price, low favourable E-factors[14] and high productivity. This last factor (the amount of substance produced per unit reactor volume per unit time) which is often ignored in laboratory studies, is crucial in all large-scale processing. As these advantages of Br_2 cannot be matched by other bromine sources. Viable industrial oxybromination reagents must feature alternative benefits. Examples of such processes include: (*i*) oxidative bromination using alkali metal bromates, which facilitate the reaction of deactivated aromatics (*e.g.* $PhNO_2$ or PhCHO which react only sluggishly with molecular bromine);[15] (*ii*) *in situ* recycling of HBr waste from Br_2 brominations; (*iii*) oxybromination using alkali metal bromide salts with concurrent recycling of other acid waste; and (*iv*) possibly certain enzymatic reactions. Note that current *ex situ* HBr recycling technology cannot compete with bromine on a simple cost basis.[16]

Oxybromination using haloperoxidase enzymes

Biohalogenation is receiving increasing attention as more halometabolites are discovered[17] (especially in the marine environment[17b]) and the properties of haloperoxidase enzymes are elucidated.[18] These enzymes are known to catalyse the two-electron oxidation of X^- (X = Cl, Br, I) in the presence of aqueous hydrogen peroxide, and to effect the oxidative halogenation of various compounds under sea-water conditions. One can therefore envisage bioreactors which would take in ocean water, hydrogen peroxide and benzene into one end, and produce bromobenzene out of the other. Note, however, that although this oxidation of Br^- occurs in a near-neutral medium, an acid is still required. In fact, recent studies on vanadium bromoperoxidase (V–BPO) models evidence that the mass-balance of oxidative halogenation requires two equivalents of H^+ (Scheme 2).[18b,c] Even for electrophilic substitution by Br^+, one external equivalent of H^+ is still needed. This means that any oxybromination system has to include a source of *at least* stoichiometric amounts of acid (in the laboratory, all oxidative halogenation reactions proceed faster at lower pH, and six-fold excesses of HCl are routinely employed to effect full conversion in oxychlorination processes[19]). Haloperoxidase enzymes, which can only operate under dilute conditions, are limited to the production of a 'Br^+' reagent in a system that contains vast amounts of water. This 'positive bromine reagent' can be either $\{enzyme–Br\}^+$, HOBr, BrO^-, Br_2 or Br_3^-, depending on $[H^+]$ and $[Br^-]$ in the reaction medium (a naked Br^+ ion would be



Scheme 2 Oxygen transfer cycle from hydrogen peroxide to 'V–BPO' followed by two-electron oxidation of bromide and electrophilic aromatic substitution. It is not certain whether for the enzymatic system the 'Br^+' remains coordinated to the enzyme or not.

unlikely except in a very acidic medium).[20a] However, can haloperoxidases (or their mimics) be used for the bromination of inactivated substrates? The impressive TOFs associated with these catalysts are invariably based on measuring changes in the absorbance spectra of Phenol-red, dimedone (DMD) or monochlorodimedone (MCD), which are all extremely reactive to electrophilic substitution. This method quantifies the enzymes' ability to oxidise Br^-, but does not guarantee its efficacy in brominating inactivated aromatics. The elegant experiments of Ryabov and coworkers evidenced, for example, in the case of the heme chloroperoxidase derived from *Caldariomyces fumago*, that the interaction between the enzyme and the organic substrate is kinetically insignificant and halogenation occurs as a result of the electrophilic attack of the active brominating species.[20b] Note also that most aromatic and heteroaromatic parent bromometabolites are phenols, anilines, and their derivatives.[17a]

Most of the reports examined above claim to study haloperoxidase reaction mimics, but this claim may be questioned. Using vanadium salts with H_2O_2 mimics vanadium bromoperoxidase to the same extent as oxygenation catalysed by iron salts is a model of cytochrome P450 monooxygenase. The major difference between the enzymatic and the H_2O_2–M systems is that substrate and reagent concentrations are μM–mM for the former *vs.* M for the latter. Haloperoxidases work well at low acidity (v_{max} at $5 < pH < 6$) and low halide concentrations, but are destroyed by H_2O_2 concentrations of over 5%,[17a] while concentrations of 35–70% are routinely employed in the laboratory for reactions catalysed by metal complexes. Furthermore, it may well be that the active catalyst in the case of vanadium salts in solution is a dimeric species,[10b] while the enzyme is reported to contain only one vanadium atom per active site. If a given synthetic approach follows a similar mechanism to that of an enzymatic reaction, it may be acceptable to consider the process as 'biomimetic'. However, it should be recognised that the extent of biomimicry strongly depends on the conditions which are employed.[21,18b]

Conclusions

Considered separately, peroxide-mediated bromide salt oxidation is currently not a viable option for large-scale bromination, as the requirement for stoichiometric acid as a reagent raises reagent prices and increases waste by-products. Although it seems that haloperoxidase enzymes catalyse oxybromination under neutral conditions, an acid is still required. The major problem with aromatic oxidative bromination is not the generation of a 'positive Br' species, but the low reactivity of this species in the aqueous environment.

Experimental

Materials and instrumentation

Chemicals were purchased from commercial firms (>98% pure) and used without further purification. GC analyses were performed using an HP-5890 gas chromatograph with an HP1 capillary column (25 m × 0.25 mm). Products were identified by comparison of their GC retention times with standard reference samples. **CAUTION!** There are hazards associated with using hydrogen peroxide.[22]

General procedure for *in situ* oxybromination

Oxybromination of anisole is described as a representative example: 10.0 mmol (1.19 g) KBr was dissolved in 10.0 g distilled water, to which was added 5.0 mmol (0.49 g of 98 wt% soln) H_2SO_4, 10.0 mmol (1.08 g) anisole, and the catalyst [0.14 mmol (26.0 mg) V_2O_5 or 0.15 mmol (26.4 mg) $Mo_7(NH_4)_6O_{24}\cdot 4H_2O$ or 0.15 mmol (17.5 mg) NH_4VO_3]. After stirring for 1 min at 25 °C, 25 mmol (*ca.* 2.5 ml of 35 wt% soln) H_2O_2 was added dropwise using a pressure-equalizing dropping funnel. The reaction was stirred (700 rpm) at 25–30 °C for 90 min, after which the organic phase was separated, extracted with diethyl ether (3 × 10 ml) and analysed by GC (*n*-decane external standard).

Acknowledgements

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Oxathiolane and dithiolane exchange reaction for carbonyl group protection: a new, fast and efficient procedure without solvent under microwave irradiation

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Protection of aldehydes and ketones as hemithioacetals or dithioacetals by an exchange reaction from 2,2-dimethyl-1,3-oxathiolane or 2,2-dimethyl-1,3-dithiolane catalyzed by solid acidic catalysts is readily achieved without solvent under microwave irradiation.

Introduction

In recent papers[1,2] we have reported various methods for solvent-free protection of carbonyl compounds and large-scale synthesis of dioxolane, oxathiolane and dithiolane under microwave irradiation.

We have shown that the exchange reaction with 2,2-dimethyl-1,3-dioxolane without solvent under microwave irradiation is a very efficient procedure for the protection of aldehydes and ketones (11 examples).

Owing to our previous work, we tried to apply the exchange reaction with hemithioacetals and dithioacetals.

The exchange reaction of dioxolane and oxathiolane was previously described in solution by Djerrassi and Gorman[3] and again by Dauben *et al.*[4] according to the following procedure: a solution of ketone, 2,2-dimethyl-1,3-oxathiolane and 10% *p*-toluenesulfonic acid was refluxed for 5 h with slow distillation of the acetone through a Vigreux column. After distillation of one half of the volume, the initial volume was restored by addition of fresh benzene and the slow distillation repeated. After an additional 5 h, the solution was cooled, treated with a solution of sodium hydrogencarbonate, dried, evaporated and the resulting hemithioacetal purified by distillation or recrystallization (yield: 34–90%, 3 examples).

The authors introduced as a hypothesis that the oxygen of the initial carbonyl group is recovered in the final product as described in the following sequence (Scheme 1).

This hypothesis excludes the formation of dithioacetal by exchange from 2,2-dimethyl-1,3-dithiolane but fits with the formation of the expected hemithioacetal and propan-2-thione.

During their study, Djerassi and Gorman[3] attempted the exchange reaction with 2,2-dimethyl-1,3-dithiolane but the reaction was reported to fail.

To our knowledge, this is the only work dealing with the exchange reaction from oxathiolane and dithiolane in the literature.

Results and discussion

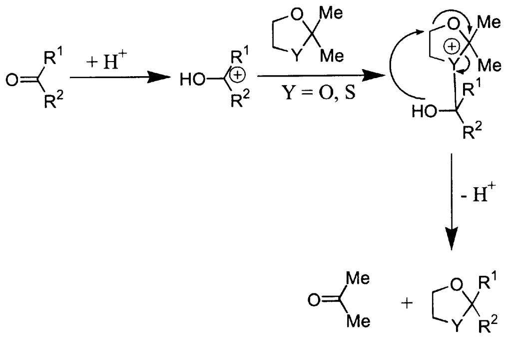
According to our previous studies related to the synthesis in dry media under microwave irradiation,[5] we attempted to set up a new procedure for the exchange reaction of oxathiolane and dithiolane based on the good results obtained with the exchange reaction from 2,2-dimethyl-1,3-dioxolane.

First, we realized a 10 mmol scale reaction starting from 2-phenylacetaldehyde **1a** and 2,2-dimethyl-1,3-oxathiolane **2a**. After optimization, the best yield was obtained after 15 min at 90 °C with 1 g of montmorillonite KSF for 10 mmol of carbonyl substrate without solvent under microwave irradiation (MWI) in a Synthewave® 402 apparatus.[6]

The same reaction for 2,2-dimethyl-1,3-dithiolane **2b** failed. This exchange reaction, however, could be completed using 10% weight Amberlyst® 15 (A15) as acidic catalyst instead of KSF.

Under these conditions we are able to convert quantitatively the 2-phenylacetaldehyde in its dithioacetal protected form **4a** in 15 min at 90 °C without solvent.

We have extended these two procedures to other aldehydes and ketones. All the results are summarized in Scheme 2 and



Scheme 1

Green Context

The protection and deprotection of carbonyl groups is often a necessary step in synthetic chemistry. Amongst the commonest protecting groups are the oxathiolane and dithiolane ring systems. Clean protection/deprotection strategies are continually being developed for such methods, and this paper describes a solvent-free route involving transfer of the protecting group from a protected acetone to the unprotected carbonyl. This liberates acetone, which could then be used in the deprotection step to reform the protected acetone. The use of a solid acid catalyst and microwave irradiation makes this a low-energy process, and allows product isolation by filtration and distillation, avoiding the need for solvent. ***DJM***

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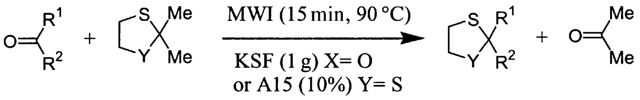
Table 1. The majority of the studied substrates led to their oxathiolane and dithiolane protected forms with good to excellent yields.



1a-h **2a**, Y= O **2b**, Y= S Y= O, **3a-h** Y= S, **4a-h**

1a: $R^1 = PhCH_2$; $R^2 = H$
1b: $R^1 = PhCH_2CH_2$; $R^2 = H$
1c: $R^1 = Ph(Me)CH$; $R^2 = H$
1d: $R^1 = MeCH{=}CH$; $R^2 = H$
1e: $R^1 = Ph$; $R^2 = H$
1f: $R^1, R^2 = C_5H_{10}$
1g: $R^1 = (Me)_2CHCH_2$; $R^2 = Me$
1h: $R^1 = Ph$; $R^2 = Me$

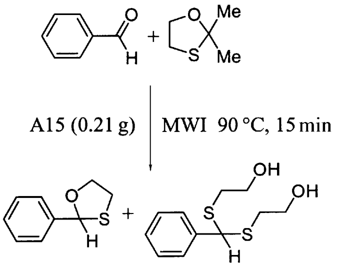
Scheme 2

Table 1 Conversion ratios and yields for **3a**–**h** and **4a**–**h**

Product	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
Conversion ratio(%)[a]	100	100	100	0[c]	97	100	70	60
Yield(%)[b]	86	72	76	0	63[d]	88	56	43
Product	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
Conversion rate(%)[a]	100	100	100	100	100	100	58	54
Yield(%)[b]	78	95	98	85	95	89	42	44

[a] The conversion rate is estimated by ^1H NMR ($CDCl_3$) (±5%). [b] Isolated product, purified by low pressure distillation. [c] Polymerization of the mixture. [d] Formation of benzaldehyde-bis(2-hydroxyethyl)dithioacetal **5e** (32%).

The oxathiolane exchange with crotonaldehyde **1d** failed owing to the low stability of the substrate towards polymerization under acidic conditions. The oxathiolane exchange with benzaldehyde **1e** led in 32% yield to the formation of benzaldehyde-bis(2-hydroxyethyl)dithioacetal **5e**. It was not possible to prevent the formation of this side product (Scheme 3).



3e: 63% **5e**: 32%

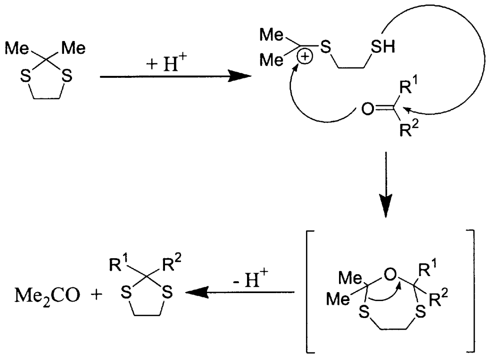
Scheme 3

The exchange reaction of dithiolane for phenylacetaldehyde **1a** has also been achieved under the same conditions (stirring, rate of temperature elevation and reactor geometry) under classical heating, in an oil bath as well as under microwave irradiation. In both reactions, the same degree of conversion was observed.

We have readily achieved the exchange reaction of dithiolane to protect several aldehydes and ketones in contradiction with the results of Djerassi and Gorman in solution. A possible mechanism for this reaction is proposed (Scheme 4).

This mechanism explains the formation of dithioacetals by an exchange reaction without excluding the possible formation of ketals and hemithioketals in a similar manner. In all the successful reactions in this study, the formation of propan-2-one was observed.

In summary, we have developed a new procedure for the synthesis of protected aldehydes and ketones as hemithioacetals or dithioacetals by exchange reaction without solvent under microwave irradiation.



Scheme 4

Conclusion

This fast and environmentally friendly procedure is efficient with a large variety of aldehydes and ketones in the absence of solvent.

Experimental

In a typical experiment, **3a** was prepared in the following manner: phenylacetaldehyde **1a** (10 mmol), 2,2-dimethyl-1,3-oxathiolane **2a** (15 mmol) and montmorillonite KSF (1 g) were introduced in the reactor (diameter: 11 mm) of the Synthewave® 402 apparatus under mechanical stirring.

The assigned temperature of 90 °C was reached in 1 min and maintained for 14 min by continuous adjustment of the power between 0 and 15 W. At the end of the reaction, the mixture was cooled to room temperature and filtered to remove the acidic catalyst. The product was purified by low-pressure distillation.

The same procedure was applied using 2,2-dimethyl-1,3-dithiolane and Amberlyst® 15 (10%, 0.21 g) to form the dithioacetals.

For **5e**, the mixture was dissolved in dichloromethane (2 ml) and filtered to remove the catalyst. After evaporation, the solid was filtered off and recrystallized from dichloromethane–hexane (50/50).

NMR (δ, $CDCl_3$) spectra were recorded on a Bruker AC 300P spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) in $CDCl_3$ with tetramethylsilane as internal reference.

2-(2-Phenylacetyl)-1,3-oxathiolane 3a

$\delta_H(CDCl_3)$: 2.88–2.98 (m, SCH_2, 2H); 2.99 and 3.23 (AB, *J* 13.8 Hz, $PhCH_2$, 2H); 3.66–3.74 and 4.23–4.29 (dm, OCH_2, 2H); 5.23 (t, *J* 5.23 Hz, CH, 1H); 7.15–7.29 (m, Ph, 5H); $\delta_C(CDCl_3)$: 33 (t, *J* 144 Hz, $PhCH_2$); 43 (tm, *J* 148 Hz, SCH_2); 64 (tm, *J* 148 Hz, OCH_2); 87 (dm, *J* 164 Hz, CH); 127 (dm, *J* 165 Hz, *p*-C); 128 (dm, *J* 160 Hz, *o*-C); 129 (dm, *J* 160 Hz, *m*-C); 138 (ws, *ipso*-C). Bp: 105 °C/1 mmHg. Yield = 86%.

2-(3-Phenylpropionyl)-1,3-oxathiolane 3b

$\delta_H(CDCl_3)$: 2.04–2.22 (dm, $PhCH_2CH_2$, 2H); 2.7–2.8 (m, $PhCH_2$, CH_2, 2H); 2.94–2.99 (m, SCH_2, 2H); 3.65–3.75 and 4.25–4.30 (dm, OCH_2, 2H); 5 (td, *J* 6, 1.3 Hz, CH, 1H); 7.12–7.28 (m, Ph, 5H); $\delta_C(CDCl_3)$: 33 (t, *J* 144 Hz, $PhCH_2CH_2$); 33 (t, *J* 144 Hz, $PhCH_2CH_2$); 38 (tt, *J* 129, 4.7 Hz, SCH_2); 71 (t, *J* 147 Hz, OCH_2); 86 (d, *J* 161 Hz, CH); 126 (dm, *J* 160 Hz, *p*-C); 128 (dm, *J* 160 Hz, *m*,*o*-C); 141 (ws, *ipso*-C). Bp: 110 °C/1 mm Hg. Yield = 72%.

2-(2-Phenylpropionyl)-1,3-oxathiolane 3c

δ_{H}(CDCl$_3$): 1.33 and 1.4 (d, *J* 7 Hz, CH$_3$, 3H); 2.78–2.95 (m, SCH$_2$, 2H); 3–3.14 (m, PhC*H*CH$_3$, 1H); 3.6–3.8 and 4.2–4.3 (dm, OCH$_2$, 2H); 5.15 and 5.2 (d, *J* 7.25 Hz, PhCHC*H*, 1H); 7.16–7.33 (m, Ph, 5H); δ_{C}(CDCl$_3$): 18 and 18.5 (qm, *J* 127 Hz, CH$_3$); 32.6 and 32.8 (tm, *J* 143 Hz, SCH$_2$); 45.8 and 46.2 (dm, *J* 130 Hz, Ph*C*H); 71.8 and 72 (tm, *J* 147 Hz, OCH$_2$); 91.7 and 92.2 (dm, *J* 158 Hz, PhCHC*H*); 127 (dm, *J* 160 Hz, *p*-C); 128 (dm, *J* 157 Hz, *o*-C); 129 (dm, *J* 159 Hz, *m*-C); 143 (ws, *ipso*-C). Bp: 108 °C/1.5 mmHg. Yield = 76%.

2-Phenyl-1,3-oxathiolane 3e

δ_{H}(CDCl$_3$): 3–3.2 (m, SCH$_2$ 2H); 3.75–3.85 and 4.35–4.6 (dm, OCH$_2$, 2H); 6 (s, CH, 1H); 7.25–7.42 (m, Ph, 5H); δ_{C}(CDCl$_3$): 34 (t, *J* 144 Hz, SCH$_2$); 72 (t, *J* 146 Hz, OCH$_2$); 87 (d, *J* 161 Hz, CH); 127 (dm, *J* 160 Hz, *p*-C); 129 (dm, *J* 160 Hz, *m*,*o*-C); 140 (ws, *ipso*-C). Bp: 90 °C/1 mmHg. Yield = 63%.

2,5-Oxathia[4-5]spirodecane 3f

δ_{H}(CDCl$_3$): 1.3–1.5 (m, cyclo., 4H); 1.7–1.9 (m, cyclo., 6H); 3 (t, *J* 5.9 Hz, SCH$_2$, 2H); 4.15 (t, *J* 5.9 Hz, OCH$_2$, 2H); δ_{C}(CDCl$_3$): 25 (t, *J* 128 Hz, C3); 25 (t, *J* 128 Hz, C4); 33 (t, *J* 143 Hz, SCH$_2$); 40 (t, *J* 128 Hz, C2); 77 (tt, *J* 147, 2.4 Hz, OCH$_2$); 96 (ws, C1). Bp: 62 °C/1.5 mmHg. Yield = 88%.

2-Isobutyl-2-methyl-1,3-oxathiolane 3g

δ_{H}(CDCl$_3$): 1.05 [d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$, 6H]; 1.45 (s, CH$_3$, 3H); 1.95 [m, C*H*(CH$_3$)$_2$, 1H]; 2.55 (d, *J* 7 Hz, CH$_2$, 2H); 3 (t, *J* 6 Hz, CH$_2$S, 2H); 4.05 (t, *J* 6 Hz, CH$_2$O, 2H); δ_{C}(CDCl$_3$): 26 [q, *J* 126 Hz, CH(*C*H$_3$)$_2$]; 28 [d, *J* 126 Hz, *C*H(CH$_3$)$_2$]; 32 (q, *J* 127 Hz, CH$_3$); 33 (t, *J* 128 Hz, CH$_2$); 36 (t, *J* 144 Hz, CH$_2$S); 71 (tt, *J* 147 2.6 Hz, CH$_2$O). Bp: 87 °C/20 mmHg. Yield = 56%.

2-Phenyl-2-methyl-1,3-oxathiolane 3h

δ_{H}(CDCl$_3$): 1.9 (s, CH$_3$, 3H); 3–3.1 and 3.15–3.23 (dm, SCH$_2$ 2H); 3.95–4.05 and 4.25–4.35 (dm, OCH$_2$, 2H); 7.2–7.9 (m, Ph, 5H). δ_{C}(CDCl$_3$): 27 (q, *J* 127 Hz, CH$_3$); 34 (t, *J* 143 Hz, SCH$_2$); 70 (tt, *J* 148, 2.3 Hz, OCH$_2$); 95 (s, Ph*C*CH$_3$); 128 (dm, *J* 160 Hz, *o*-C); 128 (dm, *J* 160 Hz, *p*-C); 129 (dm, *J* 162 Hz, *m*-C); 147 (ws, *ipso*-C). Bp: 80 °C/1.5 mmHg. Yield = 42%.

2-(2-Phenylacetyl)-1,3-dithiolane 4a

δ_{H}(CDCl$_3$): 3.1 (d, *J* 7.1 Hz, PhCH$_2$, 2H); 3.1–3.2 (m, SCH$_2$CH$_2$S, 4H); 4.7 (t, *J* 7.1 Hz, CH, 1H); 7.16–7.34 (m, Ph, 5H). δ_{C}(CDCl$_3$): 38.6 (tm, *J* 143 Hz, SCH$_2$CH$_2$S); 45.4 (tm, *J* 130 Hz, PhC*H*$_2$); 55 (dm, *J* 155 Hz, CH); 126 (dm, *J* 159 Hz, *p*-C); 128 (dm, *J* 161 Hz, *o*-C); 129 (dm, *J* 160 Hz, *m*-C); 139 (ws, *ipso*-C). Bp: 136 °C/5 mmHg. Yield = 78%.

2-(3-Phenylpropionyl)-1,3-dithiolane 4b

δ_{H}(CDCl$_3$): 2–2.15 (m, PhC*H*$_2$C*H*$_2$, 2H); 2.7–2.78 (m, PhC*H*$_2$, 2H); 3.1–3.32 (m, SCH$_2$CH$_2$S, 4H); 4.4 (t, *J* 7 Hz, CH, 1H); 7.1–7.13 (m, Ph, 5H). δ_{C}(CDCl$_3$): 35.4 (tm, *J* 129 Hz, PhCH$_2$*C*H$_2$); 38.5 (tm, *J* 143 Hz, SCH$_2$CH$_2$S); 41.3 (tt, *J* 130, 4.7 Hz, Ph*C*H$_2$); 53 (dm, *J* 152 Hz, CH); 126 (dt, *J* 160, 7.3 Hz, *p*-C); 128 (dm, *J* 159 Hz, *o*-C); 128 (dm, *J* 159 Hz, *m*-C); 141 (ws, *ipso*-C). Bp: 150 °C/1 mmHg. Yield = 95%.

2-(2-Phenylpropionyl)-1,3-dithiolane 4c

δ_{H}(CDCl$_3$): 1.42 (d, *J* 7 Hz, CH$_3$); 2.95–3.16 (m, PhC*H* + SCH$_2$CH$_2$S, 5H); 4.74 (d, *J* 8.3 Hz, PhCHC*H*, 1H); 7.17–7.31 (m, Ph, 5H). δ_{C}(CDCl$_3$): 21 (qt, *J* 127, 3.5 Hz, CH$_3$); 39 (tm, *J* 143 Hz, SCH$_2$CH$_2$S); 48 (dd, *J* 131, 3.5 Hz, PhCH*C*H); 61 (dm, *J* 153 Hz, Ph*C*H); 127 (dm, *J* 160 Hz, *p*-C); 128 (dm, *J* 157 Hz, *o*-C); 128 (dm, *J* 159 Hz, *m*-C); 144 (ws, *ipso*-C). Bp: 174 °C/1 mmHg. Yield = 98%.

2-(Prop-1-enyl)-1,3-dithiolane 4d

δ_{H}(CDCl$_3$): 1.67 (dd, *J* 6.2, 1 Hz, CH$_3$, 3H); 3.16–3.34 (m, SCH$_2$CH$_2$S, 4H); 5 (d, *J* 8.7 Hz, MeCH=CHC*H*, 1H); 5.52 and 5.63 (ABm, *J* 14.9, 8.7, 6.2, 1 Hz, MeC*H*=C*H*, 2H). δ_{C}(CDCl$_3$): 13 (qm, *J* 126 Hz, CH$_3$); 39 (tm, *J* 143 Hz, SCH$_2$CH$_2$S); 54 (dm, *J* 154 Hz, MeCH=CH*C*H); 126 (dm, *J* 153 Hz, MeCH=*C*H); 131 (dm, *J* 158 Hz, Me*C*H=). Bp: 93 °C/20 mmHg. Yield = 85%.

2-Phenyl-1,3-dithiolane 4e

δ_{H}(CDCl$_3$): 3.17–3.47 (dm, SCH$_2$CH$_2$S, 4H); 5.59 (s, CH, 1H); 7.15–7.5 (m, Ph, 5H). δ_{C}(CDCl$_3$): 40.4 (tm, *J* 144 Hz, SCH$_2$CH$_2$S); 56 (dm, *J* 155 Hz, CH); 128 (dm, *J* 161 Hz, *m*,*p*-C); 129 (dm, *J* 163 Hz, *o*-C); 140 (ws, *ipso*-C). Bp: 112 °C/1.5 mmHg. Yield = 95%.

2,5-Dithia[4-5]spirodecane 4f

δ_{H}(CDCl$_3$): 1.35–1.45 (m, cyclo., 2H); 1.56–1.68 (m, cyclo., 4H); 1.95–2.01 (m, cyclo., 4H); 3.3 (s, SCH$_2$CH$_2$S, 4H). δ_{C}(CDCl$_3$): 25 (tm *J* 128 Hz, C4); 26 (tm, *J* 126 Hz, C3); 39 (tt, *J* 143 Hz, *J* 3 Hz, SCH$_2$CH$_2$S); 43 (tm, *J* 126 Hz, C2); 69 (s, C1). Bp: 85 °C/1.5 mmHg. Yield = 89%.

2-Isobutyl-2-methyl-1,3-dithiolane 4g

δ_{H}(CDCl$_3$): 1 [d, *J* 6.5 Hz, (C*H*$_3$)$_2$CH, 6H]; 1.76 (s, CH$_3$, 3H); 1.8–1.9 [m, (CH$_3$)$_2$C*H*, 1H]; 1.93 (d, *J* 5 Hz, CH$_2$, 2H); 3.3 (s, SCH$_2$CH$_2$S, 4H). δ_{C}(CDCl$_3$): 24 [qm, *J* 125 Hz, (*C*H$_3$)$_2$CH]; 27 [dm, *J* 127 Hz, (*C*H$_3$)$_2$*C*H)]; 33 (qm, *J* 129 Hz, CH$_3$); 39 (tm, *J* 143 Hz, CH$_2$); 53 (tm, *J* 127 Hz, SCH$_2$CH$_2$S); 67 (s, CH$_2$*C*CH$_3$). Bp: 71 °C/1 mmHg. Yield = 42%.

2-Phenyl-2-methyl-1,3-dithiolane 4h

δ_{H}(CDCl$_3$): 2.11 (s, CH$_3$, 3H); 3.26–3.4 (m, SCH$_2$CH$_2$S, 4H); 7.17–7.24 and 7.7–7.75 (m, Ph, 3H + 2H). δ_{C}(CDCl$_3$): 34 (q, *J* 130 Hz, CH$_3$); 40 (tt, *J* 143, 3.3 Hz, SCH$_2$CH$_2$S); 69 (s, Ph*C*CH$_3$); 127 (dm, *J* 158 Hz, *o*-C); 127 (dm, *J* 159 Hz, *p*-C); 128 (dm, *J* 160 Hz, *m*-C); 146 (ws, *ipso*-C). Bp: 115 °C/1 mmHg. Yield = 44%.

Benzaldehyde-bis(2-hydroxyethyl)dithioacetal 5e

δ_{H}(CDCl$_3$): 2.66 and 2.8 (ABt, *J* 13.9, 6 Hz, SCH$_2$, 4H); 3.2 (s, OH, 2H); 3.7 (t, *J* 6 Hz, C*H*$_2$OH, 4H); 5.1 (s, CH, 1H);

7.25–7.46 (m, Ph, 5H). δ_C($CDCl_3$): 35 (t, *J* 140 Hz, SCH_2); 53 (d, *J* 154 Hz, CH); 62 (t, 146 Hz, CH_2OH); 128 (dm, *J* 160 Hz, *m*-C); 128 (dm, *J* 160 Hz, *p*-C); 129 (dm, *J* 162 Hz, *o*-C); 140 (ws, *ipso*-C). Mp: 65 °C. Yield = 32%.

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