Role of modern chemistry in sustainable arable crop protection

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Organic chemistry has been, and for the foreseeable future will remain, vitally important for crop protection. Control of fungal pathogens, insect pests and weeds is crucial to enhanced food provision. As world population continues to grow, it is timely to assess the current situation, anticipate future challenges and consider how new chemistry may help meet those challenges. In future, agriculture will increasingly be expected to provide not only food and feed, but also crops for conversion into renewable fuels and chemical feedstocks. This will further increase the demand for higher crop yields per unit area, requiring chemicals used in crop production to be even more sophisticated. In order to contribute to programmes of integrated crop management, there is a requirement for chemicals to display high specificity, demonstrate benign environmental and toxicological profiles, and be biodegradable. It will also be necessary to improve production of those chemicals, because waste generated by the production process mitigates the overall benefit. Three aspects are considered in this review: advances in the discovery process for new molecules for sustainable crop protection, including tests for environmental and toxicological properties as well as biological activity; advances in synthetic chemistry that may offer efficient and environmentally benign manufacturing processes for modern crop protection chemicals; and issues related to energy use and production through agriculture.

Keywords: crop protection chemicals; modern chemistry; *E*-factors; environmental quotient; biofuels

1. BACKGROUND AND INTRODUCTION

For over half a century, organic chemistry has been the mainstay of crop protection strategies for arable farming and food production. The control of fungal pathogens, insect pests and weeds has made a crucial contribution to food provision worldwide by ensuring the harvested yield of the world's crops. As we make progress in the new millennium, it is timely to take stock of the current situation and to look forward to future improvements that may be provided by new chemical technologies. There are three major aspects to be considered in this review. Firstly, we shall deal with advancements in the discovery process for new molecules for crop protection in which the chemistry is guided by experiments that indicate the properties which constitute premium products that contribute to agricultural sustainability. These include tests that provide early information on environmental and toxicological properties as well as the spectrum of biological activity. Secondly, we shall review advances in synthetic chemistry that are providing efficient and environmentally benign manufacturing processes for modern crop protection chemicals. Thirdly, we shall briefly describe recent interest in non-food crop research, with emphasis on the potential of agriculture to provide fuels from renewable resources that are advantageous in terms of net carbon dioxide contribution to the atmosphere.

(a) *World agriculture in context*

Approximately 11% of the world's land area is used for arable farming. At the aggregated global level, the increase in land under the plough between 1985 and 2000 was approximately 5.5%, i.e. less than 0.4% *per annum* increase (table 1; FAOSTAT 2004 data, <http://faostat.fao.org>).

During this period, the world's population grew by 24% overall and the aggregate gross amount of food produced outstripped this very considerably. In figure 1, FAOSTAT data (taken back to 1965) have been used to provide a measure at the global level of the intensity of agricultural production, by plotting the ratio of the food production index and the amount of land used in its production, versus the year. The intensity, thus measured, has roughly doubled since 1965.

Some important messages are suggested by these trends. Firstly, food demand has been successfully met by intensification on a fairly constant amount of land with a consequent saving of land from the plough. This trend will need to continue into the future or we shall need to convert more land area to agricultural production. Secondly, the appetite for food has outstripped population growth, presumably due to an increased desire for better quality, variety and convenience—including an increased market in emerging economies for meat and animal products, these representing generally less efficient uses of crops. We should note that technology, including fertilizer use and plant breeding as well as crop protection chemicals, has to date enabled food production to exceed population growth, while observing that food

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Table 1. Changes in world figures for land under cultivation, human population and the food production index, 1985–2000. (FAOSTAT 2004 data, <http://faostat.fao.org>.)

total land area = 13 billion hectares (ha)	1985	1990	1995	2000	% change 1985–2000
land under cultivation ^a (billion ha)	1.44	1.46	1.48	1.52	5.5
population (billions)	4.89	5.28	5.68	6.07	24.1
food production index (1999–2001 base)	72.6	80.6	87.6	100.2	38.1

^a For production of arable and permanent crops.

distribution is uneven across the world (Evans 1998; Atkin & Leisinger 2000). Thirdly, we should recognize the contribution made by the abundant availability in many countries of affordable, attractive and wholesome food to the general health of the population.

For some time into the future, chemical inputs will be vital and obligatory to maintain and improve yields. Optimized yields make a major contribution to agricultural sustainability. Loss of yield in one area needs to be replaced by imports of food and materials with consequent use of fuel for transportation, and this is in addition to expansion of the land area required to provide an equivalent crop yield.

Whereas crop protection treatments are available for almost all of the problems that affect crops, improvements in performance are required to achieve sustainability goals and this review will discuss avenues for achieving these.

(b) Crop protection technologies: the competitive environment

Notwithstanding the contributions made to agriculture by the chemical technologies, the future for chemical crop protection is subject to a number of pressures that could result in a reduction of new chemical entities reaching the marketplace (Bird 2006). The regulatory hurdles that form a necessary part of the licence to sell are ever increasing. Whereas this is a natural and in many cases desirable trend, it is regrettable that some legislation is neither science based nor evidence based, for example in cases where acceptable exposure levels to specific chemicals are based upon hazard levels rather than on a detailed risk assessment. A pertinent example is provided by the European Community Drinking Water Directive (80/778/EEC), which required that the maximum allowable concentration of pesticide in drinking water is $0.1 \mu\text{g l}^{-1}$ (approx. 0.1 ppb), irrespective of the properties, including toxicity, of the chemical residue (Finney 1994).

Furthermore, consolidation in the agrochemical industry has resulted in a situation where only six companies possess a truly global research and development effort dedicated to the invention of new chemical entities, and the pace of chemical invention in the industry is reduced. This consolidation has been largely due to the escalation in the costs of researching, developing and launching new treatments and the need to remunerate these costs by increased sales in a crowded market experiencing volatility in crop prices (Pragnell 2003).

Another relevant feature of the industry is that, for the first time, there has emerged a successful widely applicable alternative to chemical technologies. Since 1996, biotechnology has contributed to the commercial development of gene-based self-protection of plants,

Figure 1. Intensity of agricultural production 1965–2000.

where crops are genetically modified to express insecticidal and fungicidal proteins or resistance to a herbicide. In addition to both the biological and economic effectiveness of such strategies (Duke 2005; Gianessi 2005), there is great advantage in that sophisticated technology is embedded in the seed, which, in turn, can be grown by conventional local farming practice. This elegant placement of the technology can be seen as a powerful extension of chemical seed treatments and presents an alternative to spraying. The adoption of such gene-based technologies by farmers and growers has been unprecedented, as indicated in figure 2 (James 2004), which plots the increase in the area planted with genetically modified crops from 1996 to 2004. It should be noted that the success of the technology to date has been based on a small number of crops and a handful of traits. Nevertheless, there has been a significant degree of substitution of chemical treatments in these crops.

Mention must be made of the importance of classical genetics in the breeding of new commercial varieties to provide crop plant varieties exhibiting resistance to pests and improved yields. Advances in genomics can also now provide genetic markers for desirable traits, thus improving the efficiency of the conventional breeding process.

Another chemistry-based alternative to conventional crop protection treatments is provided by the use of semiochemicals, such as pheromones and food attractants. Such methods can provide a number of advantages in terms of sustainability. Typically, semiochemicals are relatively simple naturally occurring organic molecules that could be provided by biosynthesis as well as conventional organic synthesis. They are highly active and very species specific. In spite of these advantages, these methods have enjoyed relatively limited success to date and are often best suited to niche uses such as applications in confined environments or in monitoring pest populations. This topic is reviewed elsewhere in these volumes, as are aspects relating to precision breeding of new varieties.

Figure 2. Land area devoted to four GM crops 1996–2004.

Figure 3. Development of resistance to crop protection chemicals over time.

The challenge for the future is to develop optimized combinations of chemical, gene-based and biological control methods to provide sustainable integrated crop management regimes relevant to the widely differing agricultural practices across the world.

(c) *The future for chemistry in crop protection*

In spite of the foregoing, there is no doubt that chemical strategies will form the mainstay of crop protection for the foreseeable future. Most importantly, this is because there is no widely applicable alternative to chemical herbicides on the technology horizon—herbicides constitute over half of the market for crop protection chemicals. However, the industry will need to introduce new chemicals to fit in with the changing agricultural environment. The design, characteristics and manufacture of such new molecules form an important part of this review.

There are further reasons to explain why chemical treatments will achieve success in the coming years. The development of resistance by pests and weeds to current molecules will ensure that new products displaying novel biochemical modes of action will be highly prized. Resistance to families of insecticides and fungicides is already widespread, and crop protection has relied upon continued elaboration of new molecules. Even in the herbicide arena, commercial levels of resistance are now appearing (Powles & Shaner 2001), as demonstrated in figure 3 (based on

data taken from Heap (2006)). Glyphosate, by far the world's most used herbicide, is beginning to display this effect (Lorraine-Colwill *et al.* 2002). The latter finding is potentially very serious in that engineered tolerance to glyphosate forms the basis of the vast majority of herbicide-resistant crops. In spite of a massive amount of discovery research over three decades, the industry has been unable to identify a replacement herbicide with properties as advantageous as glyphosate. The broad weed spectrum, the environmental profile, the benign toxicology and the economics of glyphosate usage present a formidable target for replacement by a resistance-breaking molecule with a novel mode of action—but the rewards would be substantial.

Products with novel modes of action are characterized by rapid uptake in the market and can command premium prices. As such, they represent prime targets for invention. The key question is whether the industry, with a much diminished number of players dedicated to invention of new molecules, can keep pace with the development of resistance. This represents a serious and understated challenge to food security. It also provides a real opportunity to companies that pursue successful innovation strategies.

Notwithstanding the remarkable recent success of gene-based strategies, most crop protection situations require control of a number of pest organisms. This challenge can be met by stacking multiple genes, and this is currently a very active area of research and

Figure 4. Chemical structure of azoxystrobin (1).

development. However, the breadth of spectrum of a chemical can be highly advantageous, provided that there is sufficient safety for non-target organisms. An example of this is provided by the broad-spectrum strobilurin fungicides, which are illustrated in more detail in §3b. By 2002, azoxystrobin (1; figure 4; Godwin *et al.* 1992) had been registered for use on 84 different crops in 72 countries, representing over 400 crop/disease systems. It is clear that the amount of genetic modification or breeding that would be required to reproduce this spectrum of activity would be formidable. It is thus highly likely that safe, efficient new molecules with new modes of action will find a place in agriculture for many decades to come.

2. REQUIREMENTS OF MODERN CROP PROTECTION CHEMICALS

It was emphasized earlier that the regulatory framework pertaining to the introduction of new molecules is placing escalating demands upon the research and development process. It is clearly imperative that new molecule introductions meet the stringent requirements relating to human health and environmental protection in addition to effectiveness. Factors that are important to sustainable farming are now key drivers in discovery regimes, as are the requirements for inclusion in integrated crop management programmes. Thus, the invention process has needed to be adapted not only to meet these requirements but also to provide safety factors of several orders of magnitude. As a consequence, new indicator tests have had to be developed for introduction into various stages of the process.

(a) *Characteristics of a successful modern crop protection chemical*

The invention process starts with two key requirements. First is the choice of a target that fits the strategy of the organization undertaking the development and which is defined in terms of the biological effect required to deliver the desired benefits. Second is the elaboration of chemistries that provide the profile of a premium product. This profile includes supporting the sustainability of the whole chain of food production activities.

We ask much of candidate molecules on the path to becoming a successful product:

- survive the spray environment (sun, heat, rain),
- penetrate the organism (weed, fungus, insect),
- transport to the target (protein) and inhibit effectively,
- resist metabolism by the organism,
- avoid affecting non-target species, especially the crop,

- be benign in the environment,
- display no adverse health effects,
- be cost effective to formulate and manufacture,
- preferably possess a new mode of action, and
- provide economic returns and social benefits.

It is clear that the optimal set of molecular properties for one of these processes is likely to be suboptimal for all the others. This partly explains why it is so difficult to invent a new crop protection chemical—the process requires a continuous trade-off of properties. In addition to the factors that impart biological efficacy, it will be clear that a benign profile in terms of safety to humans and the environment is essential. Indeed, a reduced-risk pesticide registration programme is in operation in the USA in which the primary objective is to give priority and accelerated approval to products with more favourable risk characteristics than those currently available (Racke 2003). Such requirements provide the motivation to ensure at an early stage that all the required safety factors are used to guide the synthesis programme. This entails the development of rapid indicator tests to direct the chemistry efficiently into favourable areas.

(b) *Efficacy*

Potency against the target pest species is a critical property. The advantages of potency can include the following.

- Lower application rate in terms of the amount of chemical used per hectare.
- Lower volume to be applied.
- Less formulant, adjuvant and packaging.
- Smaller manufacturing and formulation plants, which can also mean less pressure on manufacturing cost, allowing more flexibility with regard to synthetic route.

Potency can also provide the potential for enhanced profitability, thus removing some uncertainty from the development process.

A great advantage of research into new agrochemicals is that, in contradistinction to pharmaceuticals, it is possible to establish *in vivo* screens to give an early realistic read-out of efficacy in the practical context. This is additional to *in vitro* tests that have particular utility in unearthing new mode of action targets.

(c) *Mode of action*

Whereas many of nature's biochemical processes are ubiquitous, some are restricted to particular orders or species. For example, many biosynthetic pathways to amino acids are absent in animals, thus providing a potential mechanism for selective toxicity through differential modes of action, with the benefit of improved human safety.

Developments in genomics have allowed significant advancement in the delineation of critical modes of action in pest species. The sequencing of the genome of the model plant, *Arabidopsis thaliana*, has led to development of important tools and novel experimental approaches, including single-gene knockouts throughout the genome (Somerville & Koornneef 2002).

This permits the pinpointing of critical genes and subsequently allows identification of proteins with essential functions. In turn, these proteins can form the basis of *in vitro* tests, against which libraries of diverse chemicals can be screened.

The first genome to be sequenced for a crop plant, rice, was completed in 2001 and published in 2002 (Goff *et al.* 2002). From these initial studies, it was also possible rapidly to recognize and determine the sequences of thousands of proteins in rice, but the studies of function require much more work. Genome sequencing of further crop plants can be expected to provide very significant advances in the understanding of crop biology (Paterson 2006).

Genomic sequencing of many pest and model species, including insects (Heckel 2003), yeasts (Forsburg 2001) and nematodes (Mitreva *et al.* 2005), continues to make important contributions to improved biological understanding of the targets *per se* and to development of high throughput biochemical and genetic tests.

Finally, and as mentioned in §1, compounds exhibiting novel modes of action are prized for their ability to combat the development of resistance by pests.

(d) *Uptake and translocation*

The efficiency of penetration of a candidate molecule into the plant, insect or fungus has a direct effect on potency, as does translocation to the site of action. Unlike the factors involved in the design of inhibitors, here the science is less well developed and the design is based on empirical principles (Bromilow 1994; Bromilow & Chamberlain 1995). Nevertheless, many of the physical characteristics of effective crop protection chemicals can be predicted with ever-increasing accuracy using *in silico* tools. These programmes are now highly developed and include interactive software with convenient graphical interfaces. In addition, several surrogate experimental tests have been developed, such as the use of model membranes to simulate transport across leaf cuticles. There has also been developed a good understanding of the physico-chemical parameters that are necessary for efficient translocation in many diverse organisms. Thus, it is now possible to estimate the molecular properties required for transport in phloem and to parametrize the chemical space that will define molecules which will reach a target site in phloem. This approach has been extended to include a range of physiological targets (Bromilow & Chamberlain 2000). It is evident that knowledge of the differential physiological characteristics of sites in non-target organisms will form the basis of a selectivity mechanism, again potentially leading to safer crop protection products.

(e) *Metabolism*

Insects, fungi and plants alike all employ metabolic processes to modify or eliminate foreign molecules, and in the case of pesticidal action, these processes can render a potential product ineffective by its removal. Metabolism also frequently accounts for mechanisms of resistance to chemical treatments. The prediction of metabolic fate in a welter of organisms can be modelled effectively in experimental surrogates or calculated

approximately from physico-chemical or kinetic properties such as hydrolysis rates or potential for conjugation (Clarke *et al.* 1998). However, there is no substitute for measurements *in vivo* in both non-target species and pests.

(f) *Environmental properties*

A major cost in the development of a new crop protection chemical product relates to environmental safety. In addition to safety to animal species, products must be benign to non-target species ranging from aquatic species through to beneficial insects such as bees.

The ideal persistence of a chemical is a property that has definite limits. The chemical must persist long enough to provide a premium effect but must not persist as a residue in the environment. These parameters are particularly difficult to balance in soil—generally a harsh environment for chemical stability. Fortunately, persistence is a property that is relatively easy to predict from model studies and physico-chemical data. Model experiments for soil half-life, hydrolysis and redox potential are readily established in rapid throughput format. In this way, chemistry can be guided into areas with favourable environmental properties.

An important regulatory issue rests with leaching into ground water and drinking water. As described in §1b, in Europe the upper limit for the amount of pesticide residue allowed in drinking water is set in terms of hazard rather than risk at $0.1 \mu\text{g l}^{-1}$ (approx. 0.1 ppb), irrespective of the nature or the toxicology of the residue (Finney 1994). Failure to employ evidence-based risk assessment could confound the optimal selection of candidate molecules for development—a superlative molecule in every environmental and toxicological aspect could be eliminated solely on the basis of exceeding the 0.1 ppb hazard level.

Again, it is easily possible to establish good model experimental systems for predicting leachability. These include rapid high-throughput assays based upon simple chromatography on various soil types through to large-scale lysimeter studies.

As part of the development process, there will be numerous large-scale field trials to test the effects on non-target species, and it is these that will be the major contributors to sustainable treatments and consequent regulatory approval.

(g) *Toxicology and human health*

The most important feature of a new agrochemical is that there should be no adverse effects on human health. The regulatory framework pays immense attention to this aspect, and a regime of studies, both *in vitro* and *in vivo*, in animal models is required to gain the licence to sell. In specific cases, human volunteer studies are conducted, albeit in the latter stages of development.

It is ironic that this most important factor is also the most difficult to model at the early stages of research. There are a number of *in vitro* indicators such as the Ames Test for mutagenicity, but these are incomplete indicators and often not amenable to high throughput and rapid reporting. The metabolic fate of chemicals in humans can be investigated using, for example, simulated gut fluids and blood preparations.

There is significant current interest in the application of toxicogenomics, in which changes in gene expression in response to chemical challenge can be measured in a microarray format (Pennie *et al.* 2001; Orphanides 2003; Waters & Fostel 2004). Whereas this field is at an early stage of development, one advantage is that expression arrays of human genes can be employed. It should be noted that at best the technique will only provide early alerts and normally in comparison with a known toxicological effect. Furthermore, many types of toxicology are not amenable to this approach.

Investigative toxicology employed at a molecular level holds much promise for studying human safety. Here, the molecular mechanism of a toxicological response is elucidated and the enzymes involved in the pathway are used in *in vitro* assays. Again, human proteins can be included in such tests.

(h) *Formulation and adjuvancy*

Formulants and adjuvants are used to improve the performance of crop protection chemicals largely by enhancing uptake into the target organism. However, there are a number of other advantages to be gained by application of this technology, such as modification of persistence by controlling release rates and improving physical form, for example by manufacturing gels or suspension concentrates. There has been considerable recent success derived from novel microencapsulation technology (Scher *et al.* 1998, 1999; Beestman 2003). Here, a microscopic amount of an active ingredient is encapsulated within a polymer wall. The chemical nature of the wall will dictate stability and the rate of release. It is possible to coencapsulate an opaque material such as titanium dioxide to act as a filter to prevent photodecomposition. Some microencapsulated products are amenable to freeze-drying, thus rendering an erstwhile liquid formulation into a solid, with consequent improvement in handling safety for both farm and chemical process operators.

The choice of solvents used in formulations is an important consideration, both in terms of efficacy and safety. With regard to the latter, similar issues apply to those encountered with solvents used in manufacture, as discussed in §4c.

As mentioned earlier, formulations involving the treatment of seeds with chemicals active against soil pests and diseases provide a simple yet elegant method of accurate placement, with benefits in environmental profile.

3. DESIGN AND INVENTION OF MODERN CROP PROTECTION CHEMICALS

All of the factors listed in §2 can form part of the design paradigm for a new molecule. Each will require the development or customization of indicator tests, if the chemistry is to be driven towards the desired product profile.

It was traditional in the industry for the early screens for a project to be based largely, or even exclusively, on biological efficacy. Modern requirements relate substantially to safety and sustainability in use and the ability to participate in integrated crop management. From the foregoing, it is evident that a more holistic

process would be advantageous in which all the properties required for a premium product are represented by indicator screens that should be high-throughput and rapidly reporting. If such screens are to be run in parallel with biological screens, then they must also be capable of being operated with small sample sizes.

Inevitably, holistic screens require the research teams to engage in significant amounts of method development, which within a limited budget will inevitably take effort from elsewhere, e.g. synthetic chemistry.

(a) *Strategies for discovery and invention*

Once a biological target has been selected and the appropriate indicator screens developed, there are several well-trodden ways of establishing a chemical lead, as discussed below.

(i) *Targeted screening*

In targeted screening, the screens are established to represent a commercial target and are challenged with a diverse range of chemicals. Such collections are available from combinatorial chemistry, parallel synthesis or by conventional compound preparation—the former methodologies being capable via automation of producing very large numbers of new compounds for high-throughput screening (Ridley *et al.* 1998). The important feature is that chemical inputs should be designed to meet the target profile in which the indicator tests described earlier are used to navigate the chemistry into areas of superior performance. Whereas such screens frequently unearth significant lead activity, this is followed by the complex process of optimization to provide the key characteristics required in a premium product (§2).

(ii) *Analogue chemistry*

In analogue chemistry, the starting point is known activity. This information is derived from a variety of sources, the most fertile of which is usually the patent literature. The goal is to provide analogues that possess superior or differentiated properties with respect to the original lead, including provision of analogues that address a very different biological target (e.g. of tefluthrin in §3b). Again, navigation by indicator screens is crucial as part of the lead optimization process. Whereas starting from known activity provides great benefit, analogues will share the same mode of action as the initial lead, with possible disadvantage with regard to the development of resistance by pests and weeds.

(iii) *Taking clues from nature*

Many organisms have been endowed by nature with sophisticated chemical-based defence mechanisms to preserve and expand the ecological niche of the species. In turn, natural product chemists have elucidated the chemical structures of such defence chemicals, which have then been tested for biological effects. This has frequently provided a rich source of bioactive lead molecules, but it is comparatively rare that these have the properties required for a successful crop protection product. The notable exceptions lie within the insecticide area where several useful products have been discovered. The largest of the recent

Figure 5. Chemical structures of some natural insecticides.

introductions by sales volume is spinosad (2; figure 5), a broad spectrum product obtained by fermentation of the fungus, *Saccharopolyspora spinosa* (Thompson *et al.* 2000). Abamectin (3), milbemectin (4), emamectin (as the benzoate 5) and *Bacillus thuringiensis* delta-endotoxin also currently enjoy significant use (Copping 2004) and, taken together with spinosad, account for the vast majority of sales in this class. However, natural product sales were estimated to account for less than 10% of total insecticide sales in 2004 (data available from Phillips McDougall Agriservice).

Conversely, such natural products have provided several productive leads for synthesis. Perhaps the most enduring example is provided by the synthetic pyrethroid insecticides (e.g. figure 6), which were derived from a natural pyrethroid series (6), exemplified by pyrethrin 1 (7).

(iv) Mechanism-based design

In the basic form of the mechanism-based approach, the target biochemical process can be defined at a molecular level and ideally the structure of the target protein (enzyme or receptor) should be known. A crystal structure of the protein, both native and with bound pseudo-substrates, provides the chemical topology of the catalytic site, and ligands are designed

to give inhibition. However, the design of potent inhibitors is one feature, but there are many other properties, less amenable to rational design, that need to be optimized to provide a successful crop protection chemical, as explained in §2 (Walter 2002). It is reasonable to assume that rational design has played an important role in part of the discovery process of some new products, but the authors are unaware of examples where this approach has succeeded in providing de novo a commercial crop protection product.

(b) Holistic approach

Whereas the four invention methodologies described above have been taken separately, in practice they almost always coalesce into a more holistic approach. As mentioned, the key driver is a commercial target expressed in terms of validated biology and biochemistry. Following gaining maximal information about the target, the search is then focused on chemical interventions from any source. For a new target, a combination of diverse chemical inputs, natural product leads and rationally designed molecules is employed to provide early hits on the chosen screens. These hits are ranked in terms of potential and the most promising chosen as leads. New compounds are then synthesized within the chemical space dictated by the properties of the target

Figure 6. Chemical structures of some natural and synthetic pyrethroids.

Figure 7. Chemical structures of some strobilurin analogues.

and the required characteristics of the product. For known targets there is a clear starting point, but converting such leads into potential products follows a similar process of optimization. The journey from an initial lead to a commercial product requires meeting a wide range of criteria—especially biological, environmental, toxicological and commercial—and this can easily take a decade and cost around \$100 million.

An early example is provided by the pyrethroids, described in §3a. Permethrin (8) was one of the early commercially successful synthetic pyrethroids, derived from a natural product lead (figure 6). This discovery was followed up by analogue synthesis programmes in several organizations, resulting in a large number of structurally related commercial introductions (e.g. deltamethrin (9) and lambda-cyhalothrin (10)). All of these introductions are characterized by their powerful activity against

foliar-feeding insects. Tefluthrin (11), although sharing the same structural motif and mode of action, represents a change in the commercial target in that it is a soil-active pyrethroid. This type of target presents a serious challenge to highly lipophilic pyrethroid molecules in that they bind very tightly to soil particles. In order to achieve the mobility in soil required for effective control of soil pests, a relatively high vapour pressure is needed, generated in the case of tefluthrin by incorporation of the tetrafluoroaryl group. This is a good example of the exploitation of physico-chemical properties to provide a favourable biological profile.

A more recent example is provided in figure 7 by the strobilurin fungicides that were derived from natural product leads from woodland fungi. The starting point for synthesis was strobilurin A (12), from *Strobilurus tenacellus*, a woodland fungus, and itself a fairly potent

Figure 8. Chemical structures of some strobilurin fungicides.

fungicidal compound, albeit insufficiently efficacious for field use. Strobilurin A (12) was found to be too volatile and photounstable to be used as a commercial fungicide. A programme of synthesis was initiated based upon this natural product lead. Compound (13) showed improved activity, and (14) effectively solved the photostability problem, although volatility *inter alia* remained an issue. This was resolved by synthesis of (15), a very active compound but too lipophilic to provide the translocation necessary for good foliar activity. More polar analogues were synthesized, culminating in the highly successful analogue, azoxystrobin (1; Bartlett et al. 2002).

Once again, the invention of a lead molecule with a novel mode of action acted as a starting point for the elaboration of other analogues, examples of which from several organizations are demonstrated in figure 8 (compounds 16–20).

4. EFFICIENT MANUFACTURE OF CROP PROTECTION CHEMICALS

(a) Background considerations

While the design of novel crop protection chemicals possessing superior properties is of the utmost importance, in the modern era it is also important to be able to manufacture such products cleanly and efficiently with minimal environmental damage. Of course, production of such chemicals must be profitable, but nowadays there are increasing costs associated with the treatment of chemical waste and more stringent regulations concerning environmental impact of chemical production. Therefore, it is increasingly important that processes are designed so as to minimize such effects. In the case of crop protection chemicals, this is especially important as early registration of synthetic routes militates against later adoption of superior 'clean' or 'green' synthetic approaches.

The underlying ideas behind 'green' chemistry have been put forward by Anastas & Warner (1998) and are encompassed in 12 principles, as follows.

- (i) *Prevention*. It is better to prevent waste than to treat or clean up waste after it has been created.
- (ii) *Atom economy*. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

- (iii) *Less hazardous chemical syntheses*. Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- (iv) *Designing safer chemicals*. Chemical products should be designed to effect their desired function while minimizing their toxicity.
- (v) *Safer solvents and auxiliaries*. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
- (vi) *Design for energy efficiency*. Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
- (vii) *Use of renewable feedstocks*. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
- (viii) *Reduce derivatives*. Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
- (ix) *Catalysis*. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- (x) *Design for degradation*. Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
- (xi) *Real-time analysis for pollution prevention*. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
- (xii) *Inherently safer chemistry for accident prevention*. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

Another important idea, put forward by Sheldon (2000), involves an environmental impact factor

Figure 9. Oxidation of 1-phenylethanol with chromium trioxide in the presence of sulphuric acid.

Figure 10. Oxidation of 1-phenylethanol with oxygen in the presence of a catalyst.

(*E*-factor), defined as the mass ratio of waste to desirable product resulting from a particular manufacturing process. In the oil industry, *E*-factors of approximately 0.1 are typical. However, the *E*-factor increases dramatically on going from bulk (1–5) to fine chemicals, including crop protection chemicals (5–50), and pharmaceuticals (25–100). This might be due to multistep syntheses being involved in the production of fine chemicals, use of excess reagents and use of large quantities of solvents.

Atom efficiency (Troost 1991) is another useful concept for the evaluation of the waste quantities that would be generated by alternative synthetic routes to a specific product. Dividing the relative molecular mass of the desired product by the sum total of the relative molecular masses of all substances produced in the stoichiometric equation(s) for the reaction(s) involved gives rise to the atom efficiency. There is an inverse relationship between the theoretical *E*-factor and the atom efficiency. The *E*-factor is higher if the yield is lower than 100%, while the atom efficiency is obviously lower. However, in order to evaluate the full environmental impact of alternative routes, it is also necessary to take into account the nature and quantities of reagents, solvents and energy used in the course of a chemical reaction. Also the nature of the waste produced should be taken into account. In order to take account of these factors, another concept, again put forward by Sheldon (2000), is that of an environmental quotient (EQ), for which the *E*-factor (*E*) is multiplied by an arbitrarily assigned unfriendliness quotient (*Q*).

In summary, modern methods for production of crop protection chemicals should ideally be atom efficient, be safe, have only one step with no solvent, generate minimal waste, have minimal energy requirement, be based on renewable resources and be environmentally benign. Such 'green' synthetic routes might involve use of recyclable catalysts, recyclable and more benign solvents and/or alternative energy sources. Advances have been made in all of these areas. However, commercial synthetic routes are confidential and are introduced at an early stage of the product development process (so most will not yet have benefited from the new ideas). Therefore, the examples given in the ensuing sections are largely taken from academic work that has relevance.

(b) The application of efficient catalysts

Many traditional manufacturing processes for intermediates used in synthesis of crop protection chemicals

suffer serious disadvantages. For example, some require large quantities of mineral acids (e.g. H_2SO_4) or Lewis acids (e.g. AlCl_3) as activators, which on work up may be hydrolysed with generation of large quantities of corrosive and toxic waste by-products. Some use molar equivalent quantities of active chemicals of which only a small subunit is incorporated into the desired product, leaving the rest as waste. Others give poor yields or produce mixtures of similar products, from which the desired component must be separated.

Catalysts are materials that speed up chemical reactions without themselves being changed. In principle, therefore, a catalyst can enable a reaction with a simple species without the need for a molar proportion of an active chemical carrier. For example, a traditional way of converting 1-phenylethanol into acetophenone is to use chromium trioxide in the presence of sulphuric acid (figure 9), which gives 1.07 kg of chromium sulphate waste for every 1 kg of acetophenone produced. A suitable catalyst would allow the reaction to be conducted directly with oxygen (figure 10), and the only by-product would be water. Clearly, such a catalyst has the potential to eliminate most of the waste.

In some cases, catalysts can also influence the proportions of products to favour the one that is required, i.e. the process becomes more selective for the desired product. This brings added benefits from improvement of the yield of the desired product and leads to a reduction in the amount of undesirable products, which would otherwise require energy for separation and would constitute waste. A few examples of such improvements in selectivity are given in the following sections.

(i) Regioselective chlorination of phenols

Several crop protection chemicals incorporate a *para*-chlorophenoxy subunit. An example is the herbicide MCPA (21; Ashford 1994), the precursor for the production of which is *para*-chloro-*ortho*-cresol (PCOC, 22), itself produced by chlorination of *ortho*-cresol (OC, 23; figure 11). Unfortunately, commercial phenol chlorination processes are often not very selective, producing mixtures of components that have to be separated, with concomitant problems of low yields, expensive separation stages and excessive amounts of waste.

In the chlorination of OC with sulphuryl chloride in the absence of a catalyst, PCOC is obtained in only approximately 72% yield, along with an isomeric product (*ortho*-chloro-*ortho*-cresol, OCOC, 24), in

Figure 11. Chemical structures of some *ortho*-cresol derivatives. Figure 12. Chemical structures of mesotrione, toluene and methyl *para*-tolyl sulphone.

which the chlorine is placed at a different position on the ring, unreacted OC and some doubly chlorinated product (dichloro-*ortho*-cresol, DCOC, 25; figure 11).

The *ortho* isomer and the dichloro product are unwanted by-products creating problems of separation. In the past, crude mixtures of chlorophenols were sometimes considered acceptable for low-grade applications as disinfectants, but concerns have increased about the toxic nature and environmental accumulation of some chlorinated phenolic compounds and their potential by-products, such as chlorinated dioxins, so there is need for superior chemical methodology for synthesis of pure *para*-isomers.

We have developed novel materials that are selective catalysts for *para*-chlorination of phenols. For example, chlorination of OC with sulphuryl chloride over one of our catalysts gave PCOC in 96% yield (K. Smith *et al.* 2006, unpublished data). This result represents a significant improvement over the traditional method, and commercial development is in progress.

(ii) *Regioselective methanesulphonylation of aromatic compounds*

Direct sulphonylation of aromatic compounds is one of the most important methods for the synthesis of sulphones, which are useful intermediates in organic synthesis with applications in crop protection chemicals such as mesotrione (26; figure 12; Michaely & Kraatz 1988), a major herbicide for use with corn. However, relatively little detailed attention has been paid to this reaction. In order to allow the reaction to proceed at a satisfactory rate, an activator such as AlCl_3 is usually needed, but AlCl_3 forms a 1 : 1 complex with the product and therefore has to be used in more than stoichiometric amount (Taylor 1990). In addition, yields are often poor. For example, traditional methanesulphonylation of toluene (27) affords a mixture of methyl tolyl sulphones in only 52% yield, and the desired methyl *para*-tolyl sulphone isomer (28; figure 12) represents only 33% of the product mixture (Olah *et al.* 1973), which inhibits the application of this potentially useful reaction in the synthesis of compounds like mesotrione.

Figure 13. Simple metathesis reaction.

We found that methanesulphonylation of toluene with methanesulphonic anhydride over a solid acid catalyst (zeolite H β) gave a 78% yield of sulphones of which the *para*-tolyl isomer represented 57% (Smith *et al.* 2004). Alternatively, a sodium-exchanged version of the solid produced mostly methyl *para*-tolyl sulphone (97%), though in low yield (15%; Smith *et al.* 2004). These results are very encouraging, though further work is necessary to render such processes commercially attractive.

(iii) *Regioselective reactions using metathesis*

Olefin metathesis is gaining importance in the chemical industry, mainly in the development of new pharmaceuticals and crop protection chemicals. Metathesis involves group exchange around the double bonds of alkenes (figure 13) in the presence of appropriate transition metal compounds as catalysts (e.g. various metal carbenes).

Metathesis offers more efficient routes to chemical products from inexpensive starting materials in fewer reaction steps. It can make use of non-toxic solvents and may produce less chemical waste than traditional routes. Metathesis is therefore an important approach for clean synthetic chemistry involving convenient and efficient chemical processes.

The 2005 Nobel Prize in Chemistry was awarded to Chauvin, Grubbs and Schrock for their contributions to the development of metathesis in organic synthesis. Chauvin investigated various chemical reactions using a wide range of metal catalysts. He also investigated in depth the mechanism of metathesis reactions (Chauvin & Commereu 1974). Schrock produced the first efficient metal catalysts for metathesis, the most important of which are arylimido complexes of Mo (Schrock 2004). These catalysts are very active and beneficial in the

Figure 14. Chemical structure of (+)-8-*epi*-xanthatin.

conversion of sterically hindered starting materials into products. Grubbs developed even better catalysts that contain Ru and phosphine ligands. Grubbs Ru catalysts are stable in air and tolerate various functional groups (Grubbs 2003). The second generation Grubbs Ru catalysts are even more stable and more active than the original ones and have been used in various applications, including examples of insect pheromones, pharmaceuticals, fragrances and agrochemicals (Pederson *et al.* 2002; Hejl *et al.* 2005).

Metathesis catalysts have been applied in the production of a range of crop protection chemicals, such as insect pheromones, herbicides and insecticides. For example, the synthesis of (+)-8-*epi*-xanthatin (**29**; figure 14), which inhibits the larval growth of *Drosophila melanogaster* (fruit fly), can be achieved from a commercially available lactone by ring-closing metathesis (RCM) in the presence of a Grubbs catalyst (Kummer *et al.* 2005).

(c) Alternative solvents for clean synthesis

Organic solvents are often used in organic reactions in large quantities. They are also used in various other applications such as pesticide delivery (Anastas 1994). However, some solvents are harmful to humans and the environment. Moreover, the use of solvent adds to the cost of a chemical process. Therefore, it is necessary to develop techniques that allow chemical reactions to be carried out without solvent or to find replacements for organic solvents. It would be particularly beneficial if such solvents could also improve the regioselective production of desirable products.

Some progress has been made using microwaves to allow chemical reactions to be carried out without solvent and in a relatively short time (Varma 2002; de la Hoz *et al.* 2005). However, not all chemical reactions can be carried out under microwave conditions, and solvents are still often necessary for the solvation of the reaction mixture. Therefore, more work and development are needed in order to find replacements of common organic solvents by alternative ones that are safer, non-toxic, inexpensive and easily available. Some examples of progress that has been made in this area are provided in the following sections.

(i) Ionic liquids

Ionic liquids (ILs) are organic salts with low melting points. Recently, they have been employed as substitutes for traditional organic solvents in chemical reactions. Over the past few years, room temperature ionic liquids have received attention for their promise as alternative reaction media, owing to their convenient physical properties, including low volatility, which render them environmentally friendly. Ionic liquids

imidazolium ILs (**30**) pyridinium ILs (**31**)

X = BF₄, BF₆, SbF₆, NO₃, CF₃SO₃, (CF₃SO₃)₂N, ArSO₃, CF₃CO₂, CH₃CO₂, Al₂Cl₇

Figure 15. Chemical structures of ILs.

are non-volatile, non-flammable, have large liquid ranges, have a high thermal stability, are relatively inexpensive to make and have favourable solvation behaviour, which make them useful as 'clean and green' solvents (Rogers & Seddon 2005). The most common ILs are those that contain imidazolium and pyridinium residues (**30** and **31**; figure 15).

Such liquids have been explored as solvents and/or catalysts in a number of reactions. In most reactions carried out in IL solvents to date, reaction rates were enhanced compared with traditional solvents. Moreover, high yields and better selectivities have often been achieved, even though the reasons are not always clear. The ILs can easily be separated from reaction mixtures by direct distillation of products, leaving the ILs behind to be used again (Seddon 1997).

(ii) Water

Water is an ideal solvent for the replacement of organic solvents. Water is safe, non-toxic, less-volatile than most common organic solvents, non-flammable, environmentally friendly, neutral, cheap, easy to handle and readily available in pure form. The use of water as a solvent in organic reactions is therefore a big challenge for researchers (Lindstrom 2002).

Heterogeneous chemical reactions in water between water-soluble and water-insoluble reactants are slow. However, the rate of reaction in such heterogeneous systems can be enhanced by the addition of an agent that can help reactants to transfer from one phase to the other (Goldberg 1989). The process is called phase transfer catalysis (PTC) if the reaction takes place in the organic layer, and inverse phase transfer catalysis when it occurs in the aqueous layer. The use of PCT is potentially attractive when any of the following features are important: elimination of organic solvents; replacement of flammable, dangerous and expensive reactants (e.g. NaH, NaNH₂, Bu^tOK) with inexpensive and water-soluble ones (e.g. NaOH, KOH, K₂CO₃); high reactivity and selectivity of the active species; high yields and purity of products; low cost and simplicity of the process; lowering of reaction temperature; improvement in reaction rates; and minimization of waste (Makosza 2000).

Organic solvents could also be avoided by the use of aqueous surfactants that aggregate to form micelles. This process is called micellar phase transfer catalysis and has been used successfully in some chemical reactions (Kammermeyer & Volkov 2002; Nelson 2003).

(iii) Supercritical fluids

Supercritical carbon dioxide (scCO₂) is a widely studied fluid for mediating reactions. Other supercritical

solvents including water and volatile hydrocarbons (e.g. propane and butane) have also been studied. Supercritical carbon dioxide is non-flammable, non-reactive, non-polar, inexpensive, easily available in pure form, easy to remove from the reaction mixture and recyclable. Supercritical carbon dioxide as a solvent in chemical processes offers many advantages, sometimes even including enhancement of reaction rate and improvement of selectivity. Carrying out reactions in scCO_2 is ideal for heterogeneous catalysis in which the reaction rate is independent of temperature and/or pressure. For all the above reasons, scCO_2 has been widely studied as a solvent for a wide range of chemical reactions (Jessop & Leitner 1999; Kajimoto 1999; Hyde *et al.* 2005; Wang *et al.* 2006).

5. CROP PRODUCTIVITY IN TERMS OF ENERGY INPUTS AND OUTPUTS

Whereas a comprehensive treatment of the role of agriculture in energy use and provision is outside the scope of this review, there are a number of features that relate closely to the foregoing sections. These are discussed briefly in context below.

(a) Energy considerations relating to sustainability

The sustainability of agricultural practices is dependent upon the efficient use of resources and especially those derived from non-renewable fossil fuels. Farming with reduced reliance on fossil fuels has been a driver for research into alternative methodologies—several of which are reviewed elsewhere in this issue.

Crop protection chemicals are largely produced from non-renewable petroleum-based starting materials, and the processes that are employed in their production generally use fossil fuels and produce significant amounts of carbon dioxide. Several reviews of the energy of inputs and the externalities associated with agriculture have been prepared (Pretty *et al.* 2000). There has also been considerable work on carbon flux in terms of inputs and emissions for various agricultural regimes (West & Marland 2002).

The prime purpose of crop protection chemical usage in agriculture is to protect yield. If we take a hypothetical but realistic example where use of crop protection chemicals at kilograms per hectare secure a 15% increase in yield of, for example, wheat over an untreated crop, then this can equate to 1.5 tonnes of grain. The balance of input and output energy budgets demonstrates an amplification effect with the outputted amount of useful fixed carbon far exceeding the inputs. However, the gain is mitigated *inter alia* by the total energy requirements and carbon dioxide emissions involved in the manufacture of the chemical. This has been addressed in §4, in which we underlined the importance of efficient and clean manufacture in this context. It is clear that more intensive research at early stages of the development process could pay very significant dividends. This simplified analysis also neglects any associated externality costs, for example water purification to remove residues, but there are two negative consequences of failing to achieve yield gain. Firstly, and as mentioned in §1a, any loss of yield

will need to be replaced by further agricultural activity—often incurring the ‘food miles’ of importation. Secondly, to produce a given amount of food, lower yields necessarily require more hectares to be brought into agriculture, with consequent environmental disbenefit.

Another consequence of this analysis of the energy costs of chemical inputs is to underscore yet again the importance of potency of crop protection chemicals in terms of dose per hectare, already discussed in §2b. Whereas compounds were commonly used at several kilograms per hectare in decades past, the use rates of modern chemicals today are very often in the range of tens or hundreds of grams per hectare, with a number acting at grams per hectare. A very approximate theoretical calculation based on broad assumptions has concluded that a putative theoretical use rate limit could be as low as $10^{-7} \text{ g ha}^{-1}$ (Corbett *et al.* 1984).

(b) Outputs: agriculture for sustainable energy production

As a counterbalance to the energy requirements of modern agriculture, mention must be made of the potential of agricultural biomass to provide both fuels and materials from renewable sources in a sustainable manner (Macleod *et al.* 2005). Such methods offer the added advantage of a net reduction in carbon emissions compared with fossil fuels. However, there are inevitably constraints that apply. For example, land used for biomass production will compete with that used for food and feed crops or will be derived from hitherto unfarmed areas.

Agricultural biomass can be either used directly for combustion—as indeed wood has been used historically as a source of heat—or processed to a renewable-based fuel. Available processes include fermentation of carbohydrate plant products to produce ethanol and using oilseed crops as sources of biodiesel fuel. Such activities already make a small but valuable contribution to global fuel supply (Powlson *et al.* 2005). Several countries now derive notable proportions of their needs in these ways, although much of this production is uneconomic and presently requires subsidies and incentives. However, the future success for biofuels rests on a combination of economics (e.g. the pricing of crude oil and other fossil fuels) and progress with technical innovation, for example in the development of superior catalysts for biodiesel processing (Toda *et al.* 2005). The concept of the biorefinery, in which total biomass is converted to useful product streams, is currently a topic of significant endeavour in which the economic principles and practices of petroleum refining are applied (Eisberg 2005). In this light, the potential of the plant sciences to supply raw materials and fine chemicals from a truly sustainable energy source has become a burgeoning area of research. In addition to energy crops, there are intensive research programmes underway relating to the production of biopharmaceuticals, specialty chemicals, biopolymers and nutrient-enriched foods from plants. The technology explosion which is currently embracing plant sciences will ensure rapid progress in these areas.

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GLOSSARY

- E-factor: environmental impact factor
 EQ: environmental quotient
 ILs: ionic liquids
 MCPA: (4-chloro-2-methylphenoxy)acetic acid
 Mesotrione: 2-[4-(methylsulphonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
 PTC: phase transfer catalysis
 RCM: ring-closing metathesis
 scCO₂: supercritical carbon dioxide