Forschung, Wissenschaft

Biorational Reflections in Agricultural Chemical Research*

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Abstract

The future of agricultural chemical research will be determined by three major factors: a) by the diminishing success rate of conventional synthesis and biological screening procedures; b) by the accentuating demand on agriculture to adapt its technologies to the preservation of limited natural resources, such as soil, water, energy, etc., and c) by the accelerating and impressive acquisition of new biochemical and biomolecular information on crop plants and pest organisms. All these factors will encourage the use of (bio-)rational concepts and approaches in designing efficient chemicals for crop production and protection. In addition, mid- and long-term, these chemicals will be supplemented by biotechnological solutions.

However, to make biorational methods and tools more successful than they are at present, a number of impediments have to be overcome, including the complexity of control-factors in crop ecosystems and the relevance of the biological testing procedures applied.

The different conceptual approaches and modern biorational methods are illustrated by recent practical examples from four areas of indication: insect control (sulfenylated carbamates), plant growth regulation (mediation of ethylene release), disease control (triazole fungicides) and weed control (photosynthesis-inhibiting herbicides).

Introduction

Christian Morgenstern introduced his gallows' songs with the following verse:

«Lass die Moleküle rasen,
was sie auch zusammenknobeln,
lass das Tüfteln, lass das Hobeln,
heilig halte die Ekstasen».

When strictly following this poetic advice, I would be able to fulfil my assignment with one single sentence: In the future, agricultural chemistry will continue to rely on two concepts only: the concept of good luck and the concept of organized chance.

However, I am convinced that the rapid advances in science and other factors oblige us to increasingly exploit rational approaches and methods in agricultural chemistry.

With this presentation, I intend to convey three messages:

- that agricultural research continues to be a very dynamic area of activity which offers a high potential for innovation
- that so-called biorational concepts and approaches will be playing an increasingly important role, and
- that within the frame of these endeavours, chemistry will remain an indispensable and, in many ways, *the* key science.

For reasons of expediency and personal experience I shall limit the following discussion to chemicals which are to be applied in crop protection and in the amelioration of crop growth. However, I believe that most of the arguments are also applicable to the discovery and/or improvement of chemicals to be used for crop nutrition, for the production and health of livestock, protection of stored agricultural produce, public hygiene, etc.

Future Environmental Conditions

To place the endeavours to improve the accuracy of the rational concepts and approaches into proper perspective, I shall briefly describe those three components of the future research environment which would appear to offer the necessary rationales and incentives.

There is no doubt that in agricultural chemistry, as in pharmaceutical chemistry, the success rate is diminishing. The yearly rate of worldwide introduction of new active ingredients for crop protection and plant growth regulation, as compiled from the latest edition of the «Pesticide Manual» [1] is shown in Fig. 1.

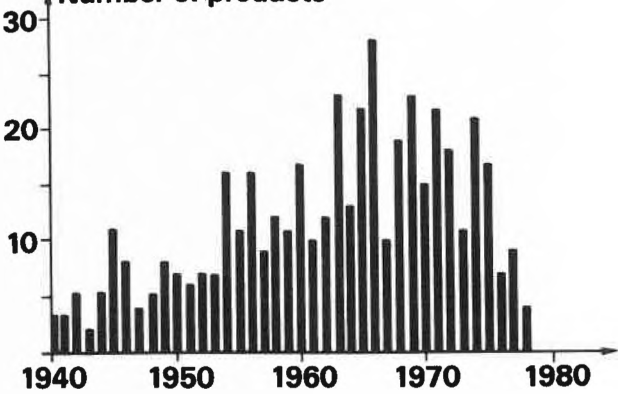

Fig. 1: Course of yearly rate of world-wide introduction of new crop protectants and plant growth regulators (active ingredients).

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* English version of a lecture presented to the Basel Chemical Society, January 26, 1984

This compilation demonstrates that the rate of introduction reached its maximum level of 20 or more compounds per year in the late sixties. Since then it has progressively declined to less than 10 compounds per year in the late seventies and early eighties — and this in spite of the fact that the number of chemicals synthesized and/or subjected to biological screening by industrial and academic institutions continues to increase. Several trend analyses, the value of which I cannot seriously contest, predict that by about 1990, no less than 70-80'000 compounds will have to be screened in a conventional manner to achieve one commercial hit [2]. These rather discouraging forecasts clearly oblige us to exploit novel and more rational concepts, reflections and techniques to the best of our ability.

Far more than in the past, crop production of the future, and, as a consequence, agricultural research, must take into account the limited availability of natural resources [3]. This imperative not only creates constraints but actually provides opportunities for exploiting rational reflections more systematically and extensively. Such phenomena as

- the erosion and deterioration of agricultural soils, not only in tropical and subtropical regions
- the diminishing availability of water, even in certain temperate zones
- the gradually increasing costs and scarcity of energy
- the real or perceived and increasingly accentuated problems of environmental pollution, etc.

do not only call for the inventiveness of agronomists and biologists but even more so for that of the chemists.

The most significant of the three environmental components described here with regard to rational concepts is the impressive and dramatic acceleration in the acquisition of biochemical and biomolecular information, both on crop plants and target organisms (Fig. 2).

This phenomenon does not only permit increasingly rational approaches in synthetic chemistry but has, at the same time, opened the gates to supplementary or even alternative *biotechnological* solutions for crop production and protection. Let me demonstrate this postulate with a simple example (Fig. 3): The lack of selectivity of several groups of broad spectrum herbicides in certain crops (prominent examples are the monocots sorghum and rice) is a significant shortcoming, i.e. upon application of the mentioned herbicides, these crops suffer either excessive damage or reduced yields. The recent introduction and anticipated further expansion of herbicide antagonists or «safeners», which are able to improve the selectivity of a number of herbicides, offer an attractive and useful chemical solution. However, on the horizon, we can already foresee biotechnological solutions for the same problems. Crops are likely to be adapted to herbicides by systematic selection, fusion and regeneration of herbicide-tolerant protoplasts or by actual gene manipulation (a statement which I shall briefly revert to later). With some imagination we can foresee crop plants which produce their own insect-controlling defense chemicals or which dispose of a genetically engineered and stable immuno-system against microbial diseases.

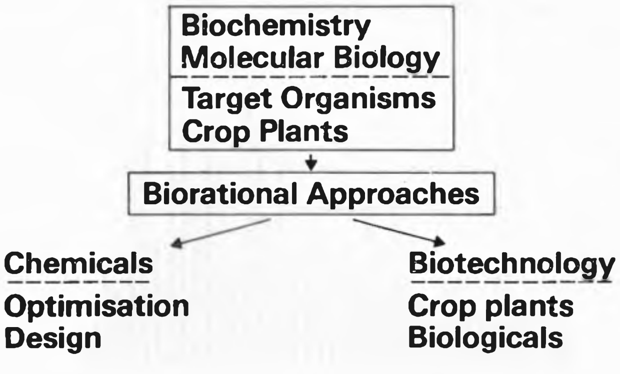


Fig. 2: Scheme demonstrating the consequences of rapid advances in plant and pest (target organisms) biochemistry and molecular biology on chemical and biochemical approaches to crop production/protection.

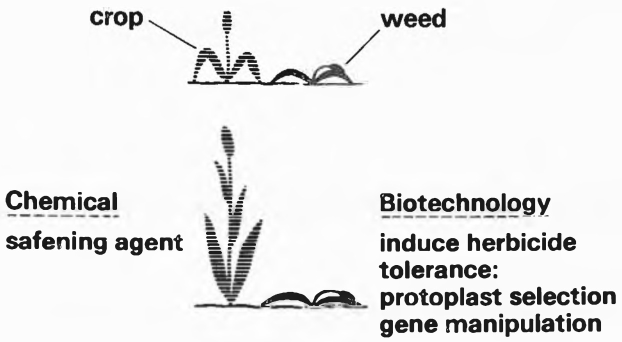


Fig. 3: Amelioration of herbicide selectivity in monocotyledonous crops by chemical and biotechnological approaches.

Definitions

The term «biorational» is utilized very ambiguously in current literature. To be clear and comprehensible, therefore, I propose to introduce a minimum set of

Table I: Definition and description of biorational approaches (optimisation and design) in synthetic chemistry, and their fit to appropriate biological testing levels.

Biology	Chemistry	Biorational
morphological	random (novel) analogy vague models	Optimisation (incl. QSAR)
physiological		
biochemical	defined models: substrate – analogs – antagonists – metabolites "de novo"synthesis	Design (incl. molecular modeling)
molecular		

definitions [4]. By the term «biorational» I mean the intellectual and experimental exploitation of working hypotheses generated from *biological* information on specific target systems.

It is evident, but surprisingly often neglected in practice, that each of these hypotheses requires a well-defined and specifically adjusted biological testing system for verification. Such systems can be classified according to four basic levels (Table 1): (1) *morphological* (i.e. the macroscopic or microscopic observation of effects on whole organisms, such as insects, weeds, etc.); (2) *physiological* (i.e. the use of separate or isolated organs, organelles, tissue cultures, etc.); (3) *biochemical* (i.e. testing systems which reflect the mode of action of specific enzymes, hormones, semiochemicals, immunosystems, neurotransmittors, electron-carriers, etc.) and (4) *molecular* (i.e. models reflecting in both chemical and physical terms, defined receptor sites on enzymes, membranes, etc.).

With the same consequence and logic, chemical concepts, methods and tools must be adapted to the chosen biological testing system. As long as testing is confined to the morphological and physiological levels, approaches in synthetic chemistry remain mainly conventional. Biorational model conceptions are rather vague at these levels and at best suited to the optimisation of recognized lead structures, whereby the different methods of quantitative structure/activity analyses (QSAR) are appropriate tools for rationalisation. For the actual biorational design of new leads in terms of substrate-analogs, -antagonists, etc., biochemical or even molecular testing systems are indispensable. At these levels, the various modern procedures of molecular modeling and computer graphics can be exploited, as shall be demonstrated later with a pertinent example.

Present State of the Art, Major Obstacles

In order to evaluate and demonstrate the present state of the art, we have attempted to subject the entire range of available structural classes of plant protection agents and growth regulators to a systematic analysis with regard to biorational reflections and approaches (optimisation and/or design) in their discovery and exploration [4]. A short-hand version of this analysis is presented in Fig. 4. The scheme demonstrates that in the four listed areas of indication (insecticides, fungicides, herbicides and plant growth regulators), more than 60 different structural classes of bioactive molecules have been introduced into practice since the early forties. With some generosity and by relying on the published case histories we have detected no more than three of these classes which had their origin in biorational reflections. An additional ten of them were, at least in part, optimised with some biorational assistance. However, the large majority of the listed classes had been discovered by conventional means, i.e. random screening and subsequent chemical optimisation.

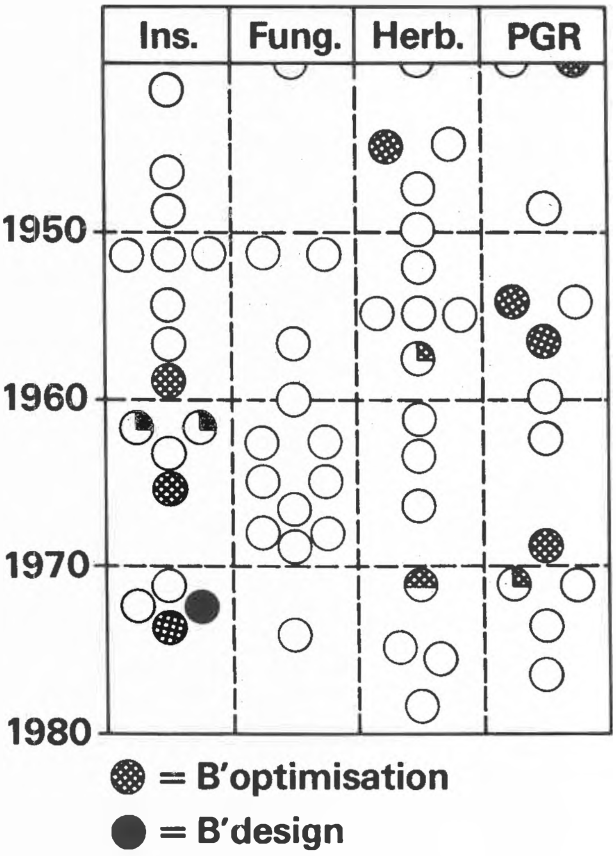


Fig. 4: Time scale of disclosure of different structural classes of plant protectants and plant growth regulators (PGR) and evaluation of biorational approaches (optimisation and design) used in their discoveries.

To make future progress, we must therefore seriously ask ourselves: Which impediments have precluded more success up to date? I believe that the agricultural chemist has been and continues to be faced with four basic obstacles or barriers, which, in order to be successful, have to be reduced or removed:

- the already discussed success rate of conventional procedures which, until recently, has been acceptable enough to discourage systematic attempts at alternative approaches.
- the multitude and variety of target organisms and the diversity of control-(loss-) factors which affect the behaviour and fate of bioactive molecules under practical agricultural conditions
- the complexity and/or irrelevance of biological testing systems, and
- a considerable and continuing lack of basic scientific knowledge, in spite of the present rapid acquisition of biochemical and biomolecular information.

In the following I shall briefly comment on the second and third impediments mentioned above.

In contrast to the pharmaceutical chemist, who can concentrate on one single mammalian species, the human being, the agricultural chemist is faced with an immense variety of target organisms and crop plants. The literature mentions more than 200 economically important insect species, diseases and weeds, which exhibit a wide range of morphological, physiological and biochemical peculiarities. Under these conditions, the identification of biorational models which reflect a sufficiently broad spectrum of activity and, at the same time, the desired selectivity, is a task in itself.

The multitude of control- or loss factors which affect and modify the behaviour and fate of a bioactive molecule in a crop ecosystem (including plant, soil and target organism) surpass in their complexity by far those of a single and closed mammalian system (Fig. 5). The interactions of such factors as volatilisation, chemical and photochemical degradation, penetration, adsorption, transport, metabolism, elimination, etc., are so complex that only some or parts of them can as yet be defined by rational hypotheses and modeling procedures. A typical example which demonstrates the composite effects of control factors is given in Table II. For many years, ever since it was recognized that herbicidal ureas and triazines inhibit the photosynthetic electron transport system (or Hill reaction), systematic efforts have been made to exploit physiological and biochemical testing systems which imitate this mechanism. As shown by the pyrrole derivative CGA 71'884 and the substituted benzoquinone DBMIB, components with inhibitory activities equal to those of the ureas and triazines have repeatedly been identified. However, as soon as these chemicals were tested further under more practical conditions, their herbicidal activity disappeared, either in the greenhouse or under actual field conditions.

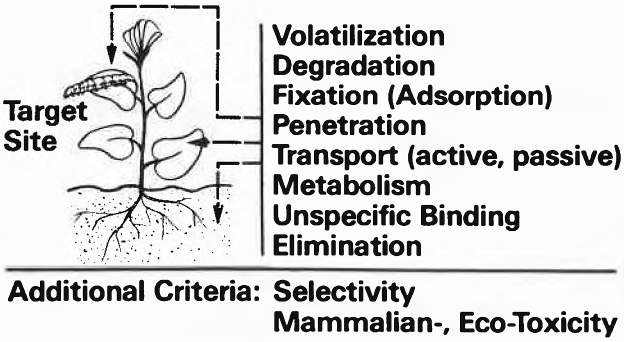
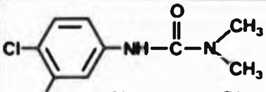
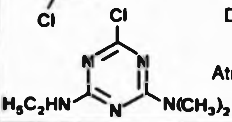
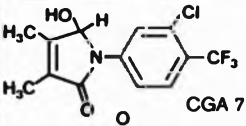
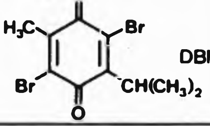
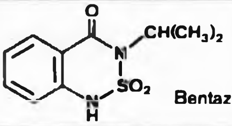
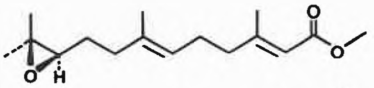


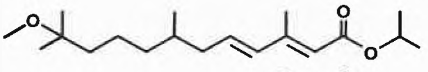
Fig. 5: Scheme illustrating the multitude of control-(loss-) factors which affect the behaviour and fate of bioactive chemicals in the pest-crop-soil ecosystem.

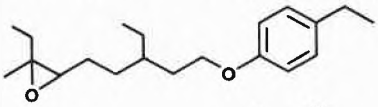
Table II: Composite effect of control-(loss-)factors on the activity of herbicides. The effect is demonstrated by comparing the inhibitory activity of the listed compounds in the photosynthetic Hill-reaction test with their herbicidal activity under greenhouse and field conditions.
CGA 71'884 = 1-(3-chloro-4-trifluoromethyl-phenyl)-3,4-dimethyl-5-hydroxy-2-oxo-pyrrole.
DBMIB = 2,5-dibromo-3-methyl-6-isopropyl-1,4-benzoquinone.

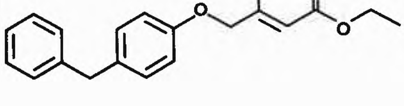
Structure	Hill-Reaction -log I50	Herbicidal Activity Greenhouse	Field
 Diuron	6,7–7,5	Good	Good
 Atrazine	6,1–6,6	Good	Good
 CGA 71884	6,2	Good	Poor
 DBMIB	6,1	Poor	–
 Bentazone	3,7–4,4	Good	Good

The importance of the *relevance* or accountability of biological testing systems with regard to subsequent practical exploitation can be documented with a number of examples. I have chosen one which demonstrates that the lack of relevance which, in this particular case, was caused by a lack of scientific information, can lead to exaggerated expectations in practice. The example deals with insect juvenile hormone analogs, a subject which has been intensively investigated for years and which has generated numerous highly active synthetic derivatives, three of which (derived from juvenile hormone III) are listed below.


Juvenile Hormone III


Methoprene


Epofenonane


CGA 13353

These juvenoids were routinely tested on the last larval stages or on pupae of various insect species (Fig. 6). The objective was to prevent pupation or metamorphosis of these larvae and to thus cause their premature death. It was not foreseen that these larvae would turn into voracious, unnaturally large «superlarvae», which, although they eventually died, continued to cause damage for an unacceptable period of time. The point to be made by this example is to un-

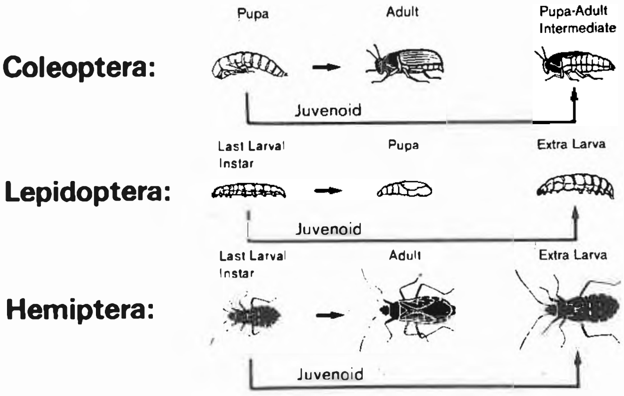


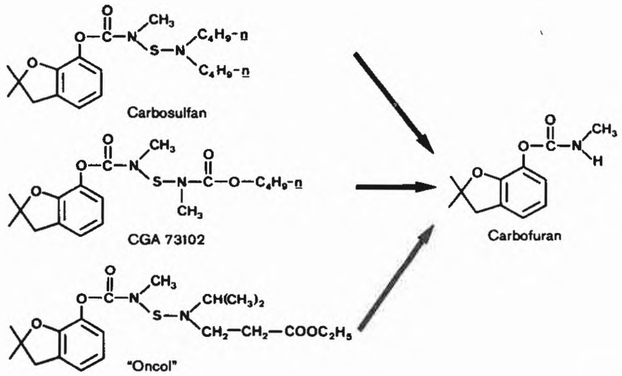
Fig. 6: Scheme summarising routine procedures used for the biological testing of synthetic juvenile hormone analogs (juvenoids) on various genera of insects.

derline that, whatever testing system is used in the biorational design of new molecules, its relevance to the envisaged biological effects and to the potential use in practice must be carefully evaluated and clearly defined at an early stage.

Selected Examples

With the following four practical examples, I shall attempt to illustrate and underline a number of the general reflections and concepts offered above.

The first and very simple example demonstrates that what were originally rather vague biorational reflections can lead to products with improved environmental properties:



The methyl carbamate carbofuran is a very effective broad-spectrum soil insecticide. However, it has a rather high acute mammalian oral toxicity of less than 10 mg/kg in the rat. By embarking on the pro-drug, or, in this case, the pro-insecticide approach, *Fukuto* [5] developed the idea of phosphorylating or sulfenylating biologically active methyl carbamates, in order to induce a differential metabolism between insects and mammals, and thus to reduce their acute toxicities. The three listed sulfenylated derivatives carbosulfan, CGA 73'102 and «Oncol» are representatives of this concept. All three chemicals are on their way to practical use, and have indeed acute toxicity values which are roughly 10 times better than that of carbofuran. The reduction of toxicity without loss of insecticidal activity has been achieved by generating additional mammalian pathways via non-toxic sulfone- and less toxic sulfide-derivatives, whereas in insects, the sulfenylated compounds are directly metabolised to carbofuran.

The second example is drawn from the area of plant growth regulation. Ethylene is one of the natural plant hormones whose involvement in ripening and senescence processes has long been recognized, and which is also presumed to regulate certain germination and vegetative growth phenomena [6]. The fact is that external applications of ethylene affect a broad spectrum of physiological events in all phases of plant growth (Table III). In practice, fruit ripening, fruit- and leaf-senescence and other processes are controlled by exposure to ethylene gas or by the application of commercial and development compounds which liberate ethylene in relatively low quantities, or at specific rates.

Table III: Effects of the hormone ethylene on various plant growth and development processes and their exploitation in practice by commercial and development compounds.

1. Vegetative Growth ●	**– apical dominance – dwarfing ● – tuber, bulb formation**
2. Flowering	**– induction**
3. Senescence (wilting) ○ Ripening ● Abscission ●	**– flowers ○ – leaves – fruits ●**
4. Various	**– dormancy, germination ○ – latex flow ○ – sex expression – root initiation**

○ = development products
● = sales products

After the major pathway of ethylene biosynthesis has been elucidated [6], additional handles for accelerating or reducing the formation of the hormone have become available (Fig. 7). The amino acid L-methionine serves as the substrate for the synthesis of the hormone. The C-3 and C-4 atoms of methionine are used in the formation of 1-aminocyclopropane-1-carboxylic acid (ACC), whereby S-adenosylmethionine has been postulated as an intermediate. This reaction is mediated by pyridoxalphosphate as a co-factor. The aminocyclopropane-carboxylic acid (ACC) either liberates ethylene with the aid of oxygen or is removed from the ethylene pathway as malonyl-derivative (MACC) in the sense of a regulatory alternative pathway.

From among the various options available for modi-

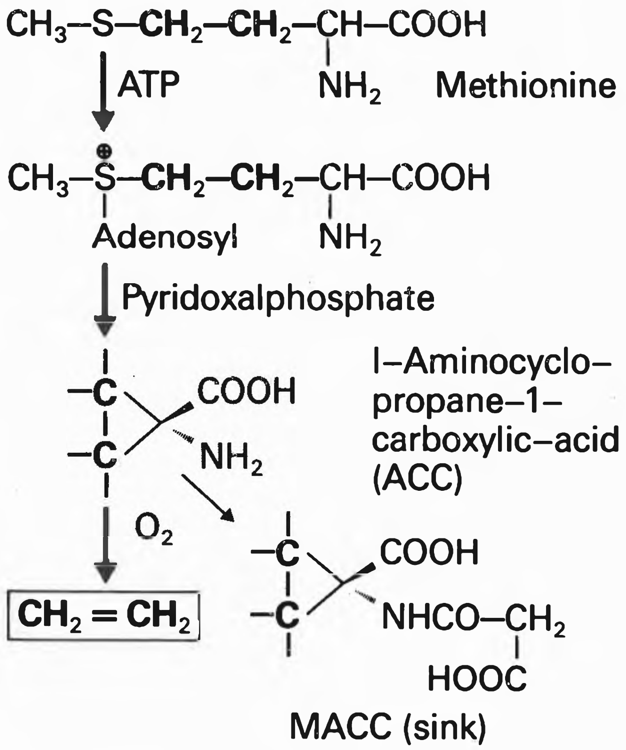


Fig. 7: Pathway of ethylene biosynthesis from L-methionine in plants.

fying the formation of ethylene by interfering with its biosynthesis, two hypotheses are mentioned which are actively pursued according to the literature and patent information (Fig. 8):

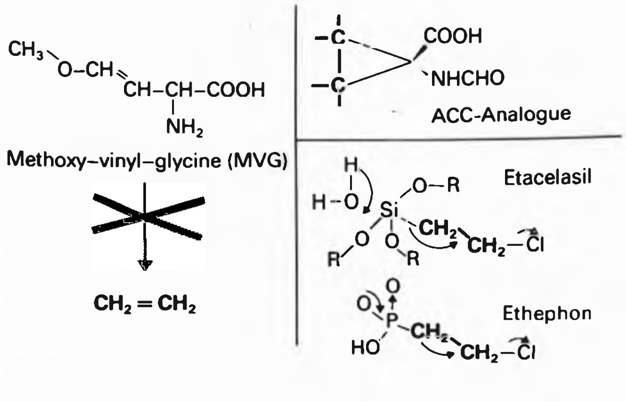


Fig. 8: Compounds which modulate the availability of ethylene in plants either by interference with its biosynthesis (MVG, ACC-analogue) or by releasing ethylene after application (etacelasil, ethephon).

- the use of enolether-amino acid analogs (such as methoxy-vinyl-glycine), which are known to trap the mentioned co-factor pyridoxalphosphate and thus to reduce or inhibit the formation of ethylene
- the application of analogs of the aminocyclopropane-carboxylic acid (ACC), which are more stable than the natural substrate, and which therefore increase the latter's pool and thus are able to accelerate the formation of ethylene.

The right hand side of Fig. 8 lists «pro memoria» the two commercial active ingredients etacelasil and ethephon, which do not regulate the biosynthesis of ethylene but which are able, as mentioned earlier, to liberate ethylene in the specific quantities required under practical use conditions.

Unfortunately, neither the enzymes involved in ethylene biosynthesis nor the receptor sites of the hormone have been characterized in sufficient detail so far. Therefore systems cannot yet be carried to the biochemical or even molecular levels.

Before proceeding to the next two examples, I suggest to make an additional general comment. For the actual biorational design of new lead structures, two basically different approaches are feasible:

- in the first approach, the starting point is provided by the mode of action of an established bioactive molecule (synthetic or natural). By rational means, new structures are then designed which have the same or the opposite mode of action at the same target site.
- in the second approach, the starting point is given by a pre-chosen natural target-site or -mechanism. In this case, structures are designed by rational means which fit this particular target.

As the third and fourth examples to be discussed below will demonstrate, present projects in agricultural chemistry are mainly confined to the first one of these approaches. For the second one, basic biochemical and molecular knowledge is still largely insufficient, as has already been illustrated by the preceeding example on ethylene modulators.

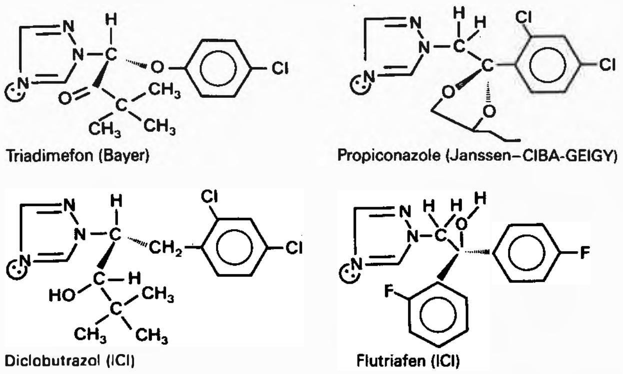


Fig. 9: Triazole fungicides which inhibit the biosynthesis of ergosterol from lanosterol.

The third example is drawn from the area of plant disease control. Following the pioneering work of Bayer AG in Germany, the triazoles have been developed into a prominent class of fungicides whose synthetic chemical exploitation is still continuing at high intensity (Fig. 9). A number of new triazole derivatives are presently under development. These compounds are systemic, i.e. they are distributed in the plant, mainly in apical direction, by the xylem system. They are active at relatively low rates of application (100-300 g/ha) and their spectrum of activity covers a wide range of economically important pathogenic fungi, including powdery mildews. Their impressive biological activity has very rapidly generated a number of systematic and detailed studies of their mode(s) of action. The major mode of action of the triazoles depends on their inhibiting the biosynthesis of ergosterol from lanosterol, thus preventing the normal formation of cell membranes. A more exact siting of the inhibitory activity demonstrated that triazoles block the first, i.e. oxidative step in the 14α-demethylation of 24-methylene-24,25-dehydrolanosterol (Fig. 10). The reaction requires, in addition to oxygen and NADPH, cytochrome P-450 as an enzyme component.

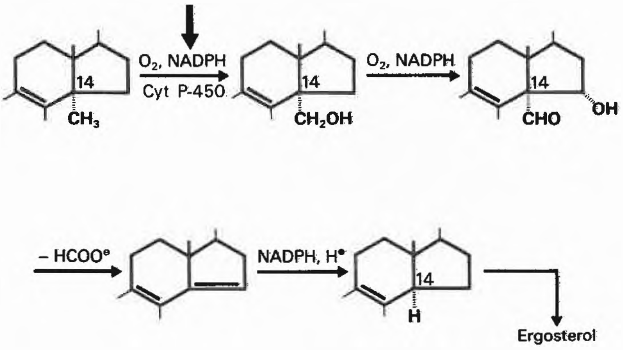


Fig. 10: Site of inhibition of 14α-demethylation of 24-methylene-24,25-dehydrolanosterol by triazole fungicides.

This information has recently been exploited in exemplary fashion in two directions:

- it has enabled, among others, *Mercer* et al. [7] to develop specific, receptor-oriented «in vitro» biochemical testing systems, which allow the routine establishment of quantitative structure/activity relationships among potential inhibitors of ergosterol biosynthesis.
- it has animated ICI-scientists, especially *Marchington* [8] to explore and define the structural elements and properties of inhibitors of the 14α-demethylation reaction by three-dimensional computer graphics.

The starting point of this second approach was provided by a rough two dimensional model of the active center of cytochrome P-450 (Fig. 11), whereby the three following features were considered to be relevant:

- the prosthetic group of the enzyme, an iron-porphyrin (heme-)ring which is available for complexation of the substrate and/or inhibitor
- the lanosterol-specific, hydrophobic binding site for the substrate in the protein-moiety of the enzyme
- the occurrence of two hydrophilic propionic acid side chains in an otherwise grossly hydrophobic environment which are presumed to intervene between the bound substrate and the heme.

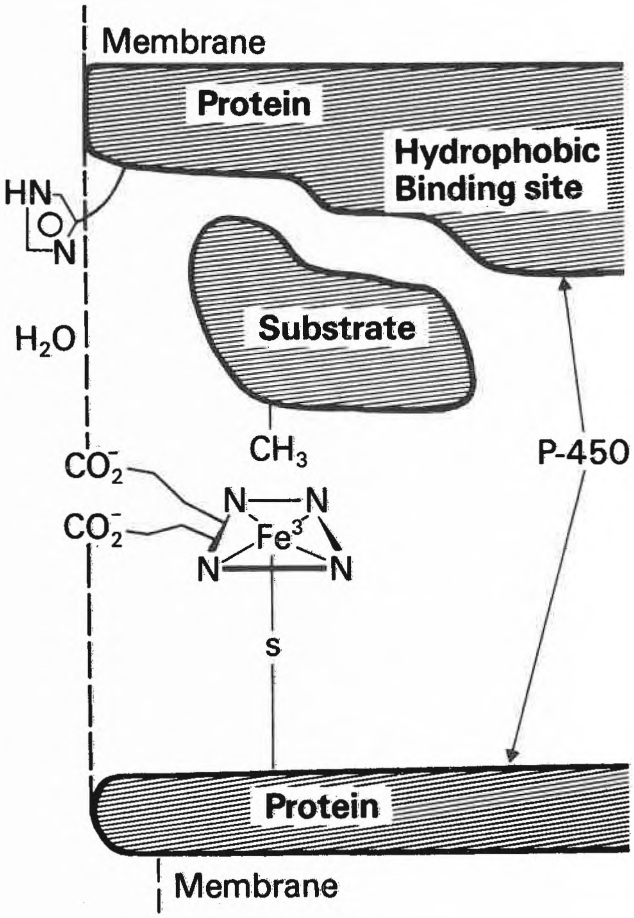


Fig. 11: Two-dimensional model of active site of cytochrome P-450 oxidase enzyme system.

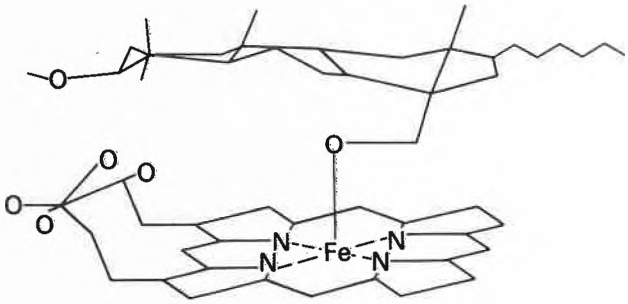


Fig. 12: Three-dimensional computer graph of orientation of lanosterol on porphyrin ring of cytochrome P-450.

These features were used, in addition to appropriate physical parameters (such as crystal structure, molecular orbitals, infrared and nuclear magnetic resonance data), to construct, with the assistance of the computer, a three-dimensional model of the enzyme-substrate (or inhibitor) complex (Fig. 12). The availability of these elements permits the description and definition of the essential electronic and stereo-electronic and steric properties of an inhibitor of the 14α-demethylation reaction for detailed examination by synthetic chemists.

The fourth and last example again commences from the mode of action of a whole class of bioactive compounds. However, in this case the conceptual approach was different from that described for the triazole fungicides and provided information with the potential of being exploited not only in synthetic chemistry but also in biotechnology.

Many of the presently used classes of herbicides, including the substituted ureas (exemplified by diuron), triazines (atrazine) triazinones (metribuzin) and uracils (terbacil) have been identified as inhibitors of plant photosynthesis (Fig. 13).

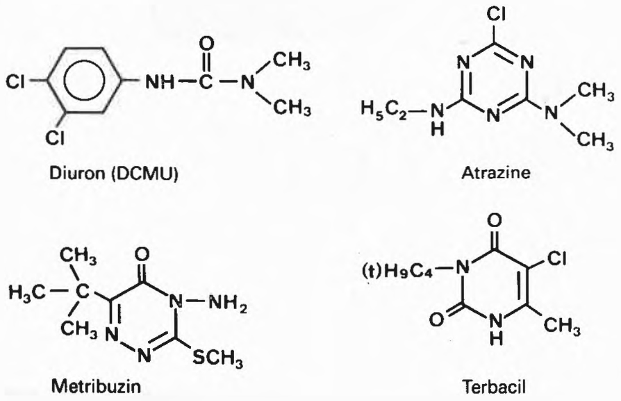


Fig. 13: Representatives of four classes of herbicides which inhibit plant photosynthesis.

The electron transport system of photosynthesis is located in the thylakoid membranes of the leaf chloroplasts (Fig. 14). It is driven by two chlorophyll-containing reaction centers (photosystems PS II and PS I) which act in series. The reaction centers utilize light energy for the oxidation of water to oxygen and for the transport of electrons, against the thermodynamic gradient, to a reductant with strongly electronegative redox potential [9, 10]. The above-mentioned classes of herbicides intervene on the so called acceptor side of photosystem II. In this part of the chain, the previously generated electrons are carried by plastoquinone molecules which are available in differently bound stages (labelled Q_A, Q_B, PQ in Fig. 14) and which transfer them to the spatially separated components of photosystem I (which comprises among others, cytochrome F and plastocyanine as electron carriers). In practice the inhibition of this part of the photosynthetic reaction, one of the major plant-specific reactions, ultimately leads to the death of weeds.

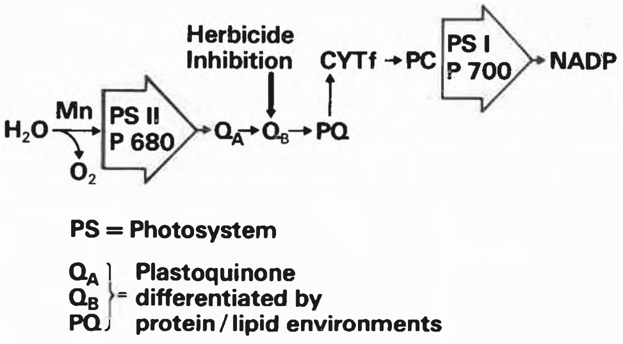


Fig. 14: Schematic summary of plant photosynthetic electron transport pathway and site of inhibition by herbicides.
CYTf = cytochrome F
PC = plastocyanine

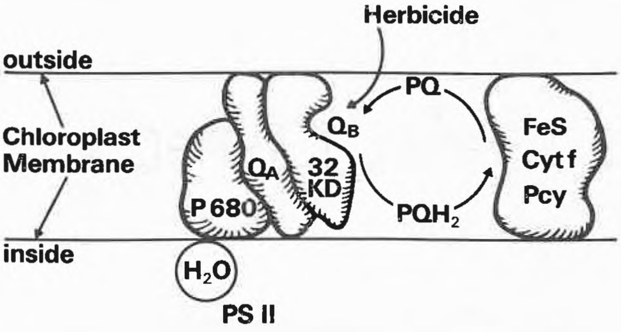


Fig. 15: Model demonstrating the structural organisation of the polypeptides and associated co-factors of photosystem II-complex in plant chloroplasts.

By using different fractionation techniques, detergents, etc. the protein complex of photosystem II has been separated into a number of discrete polypeptides, which, however, are not yet completely characterized (Fig. 15). As regards the mode of action of herbicides, particular attention has been devoted to the so-called 32 kilodalton (molecular weight = 32'000) polypeptide for the following reasons:

- Receptor studies have demonstrated that in illuminated, functioning chloroplasts, the herbicides are bound to this particular polypeptide
- Herbicides have been shown to compete with reversibly bound oxidized plastoquinone (PQ) for the same binding site and thus to prevent the formation of reduced plastoquinone (PQH_2)
- In fully functional chloroplasts of herbicide-resistant plants (i.e. plants which are not killed by the herbicide) no binding of the herbicide to the described locus has been observed.

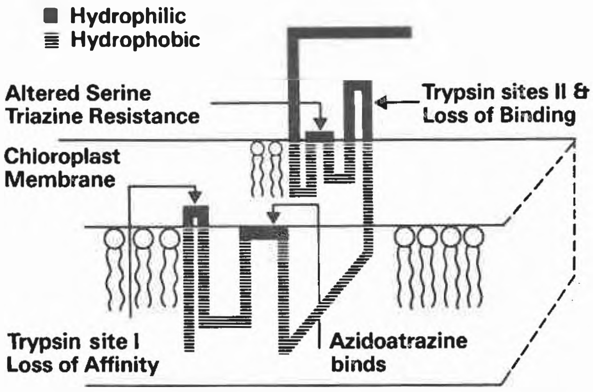
By these biochemical investigations, which were mainly conducted by *Arntzen* and his co-workers [10] the site and mode of action of the classes of herbicides under discussion have thus been described and defined in considerable detail.

Most recently, important additional information has been provided by molecular biologists, working from two directions:

- *Zurawsky* and *McIntosh* have succeeded in determining the base sequence of desoxy-ribonucleic acid (DNA) which codes for the 32 kilodalton protein in spinach chloroplasts and have thus been able to deduce the amino sequence of the polypeptide [11, 12].
- *Rao* et al. have elucidated the topographical structure of the 32 kilodalton polypeptide in the chloroplast membrane. They have been able to show that it con-

sists of 7 transmembrane hydrophobic helices which are connected by exposed hydrophilic turn segments [13].

This information which is illustrated by *Steinback's* model (Fig. 16) has permitted the localisation of the binding sites of herbicides even more accurately. At the same time it has been observed that in chloroplasts derived from herbicide-resistant plants, serine had been replaced by glycine in one of the turn segments.



Steinback et al. (in press)

Fig. 16: Model of 32 kilodalton polypeptide and herbicide receptor site of photosystem II in plant chloroplast membrane.

Such models can now be exploited in two directions:

- to the synthetic chemist, they offer the opportunity to utilize the target site information for detailed structure/activity analyses at the molecular level. However, these endeavours would be facilitated if additional physical information (such as X-ray crystal structure data) became available.
- to the biotechnologist, they provide the means for characterizing the 32 kilodalton polypeptide of herbicide-resistant, functional chloroplasts and to construct the corresponding nucleic acid which codes for it. If this nucleic acid can then be transferred to and expressed in other plants, the design of a herbicide-resistant crop species will be achieved.

Conclusions

I have attempted to describe some of the scientific concepts and methods which are pursued in agricultural chemistry and which, let us hope, will be perfected to meet the future practical requirements of crop production. In summarizing these efforts, I wish to draw the following three general conclusions:

1. The scientific advances and practical results achieved in agricultural chemistry during recent decades are in many ways impressive. However, when these results are measured against the key objectives or constraints to be met by chemicals used in crop production (such as adequate efficiency and selectivity, acceptable environmental behaviour and toxicity, avoidance of resistance phenomena, etc.) further improvements are necessary. In addition, pest populations, be they insects, diseases or weeds, are biologically very dynamic and need constant adaptations in their control. In order to solve these problems synthetic chemicals will be indispensable tools for the foreseeable future. However, in the mid- and long-term they will be increasingly supplemented by biological and biotechnological means. This concept of combined chemical and biological objectives and measures will, more than ever, call for biorational approaches and methods.
2. The predicted increase in the practical use of combinations of chemical and biological methods also enhances the pressure for interdisciplinary approaches which should not, indeed can no longer be limited by traditional educational and professional boundaries (such as chemistry - biology - agronomy). In a recent report the U.S. National Science Foundation confirms that «traditional disciplinary boundaries are dissolving between the fields of science and between science and technology» and specifically mentions that «advances in genetic engineering or in understanding plant molecular biology, depend on biochemistry and chemical engineering along with botany, medecine and agriculture» [14].
3. As far as chemistry is concerned, I believe that the examples used in this paper show that it will continue to be an indispensable discipline in agricultural research. However, the chemist can no longer afford to satisfy himself with his synthetic knowledge and craftsmanship. He must learn to cope with and master a number of supporting scientific tools, including biochemistry, molecular biology and electronic data processing.

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Schema 1: ^{13}C-NMR-Daten; chemische Verschiebungen in ppm.