Chapter 6

Propesticides and Their Implications

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Additional information is available at the end of the chapter

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Abstract

With increasing knowledge of the biochemistry and genetics of major pest insects, weeds, and agricultural pathogens, the design of such selectivity becomes a part of pesticide development and is achieved by appropriate structural modification of the parent lead molecule which is called as propesticide. In a strict sense, a propesticide is a biologically inactive compound requiring structural transformation(s) after application to become pesticidally active. Various pesticides have come to the limelight of being a propesticide by carrying out studies on their metabolic fate in organisms. Studies on the metabolic fate of diafenthiuron in vitro by liver microsomes from various vertebrates revealed a variety of possible transformations of the thiourea. Few have been developed by reversibly masking the active ingredients. Fluorinated N-acylaziridine behaves as a propesticide of the fluorinated carboxylate and the hydrolysis of the former to 2-methylaziridine and carboxylate being activation pathway. Imidacloprid and the thiazolylmethyl analogue masked with oxodioxolyl group decomposed with half life of 15.4 and 11.4 h in alkaline and physiological salt solutions, respectively, releasing imidacloprid quantitatively. New propesticide with two effects of both benzoylphenyl ureas and carbamates were designed and synthesized.

Keywords: propesticide, biologically inactive, lead molecules, oxodioxolyl, xenobiotics, selective agrochemicals

1. Introduction

Pesticide as an input in agriculture has seen changes at different stages in very few decades. Pesticides as such according to FAO may be defined as any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered

to animals for the control of insects, arachnids or other pests in or on their bodies [1]. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

Present day pesticides which are common and widely used have number of adverse affects on non-target organisms. The consequences lead to environment toxicity affecting ecosystem [2]. Therefore safer insecticide deserves attention. A propesticide is a biologically inactive compound requiring structural transformation(s) after application to become pesticidally active. Activation process for propesticides can be one of or a combination of the three following types: (a) chemical (nonenzymatic); (b) biochemical (enzymatic); or (c) physical, e.g., photochemical [3]. In practice, however, propesticidal substances are sometimes active without chemical modification when measured *in vitro*; nevertheless, their metabolites contribute significantly to the overall biological activity of the applied material.

2. Safer pesticides

Safer pesticides are those chemicals which have no or minimum acute or chronic toxicity to mammals and harmless to non-target organisms as well as non-persistent in the environment. The harmful effects of pesticides to non-target organisms can be overcome to certain extend by increasing the selectivity pf pesticide. Pesticide selectivity as such can be attained by either physical or biochemical means that is often combined in practice. In the former, only the target species is exposed to the control agent, and this can be accomplished by special formulation or precise application techniques [4]. In the later, selectivity is based on differences of the biochemical processes or target receptors of the pest and non-pest species. Furthermore, physiochemical factor such as differential uptake by and translocation within target and non-target organisms can contribute to disparate biological activities [5]. Nevertheless, differences in metabolic pathways, which convert toxic xenobiotics into less harmful and readily excretable product, and in metabolic rates of various organisms are frequently the basis of selectivity.

3. Propesticides

A biologically inactive compound requires structural transformation(s) after application to become pesticidally active. Derivatives of known active ingredients that are converted to parent compound for activity. These are various process require for the activation of propesticide to the pesticidally active one [6]. Ideally these activation processes takes place only in the target organism. Even though it can also takes place in the environment, including soil and atmosphere. These can be one of or combination of the following four types:

3.1. Activation by primary biochemical target

This activation process is carried out in presence of certain enzyme or enzyme system. Enzymatic conversion of a proinsecticide to the active toxophore at the target tissue results

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in disruption of activating enzyme [7]. The activating enzymes, present in the tissue of target organism, are carrying out certain biochemical function in the body of target organism. When active toxophore are released from the proinsecticide their normal functions are discontinued resulting in killing of organisms. This is also known as suicide inactivation as their natural process is being inactivated [8]. Likewise, there also takes place the following:

a. Disruption of secondary enzyme system in the same tissue.

b. Disruption of enzyme at other target tissue.

3.2. Activation by detoxification system

By detoxification system we meant the various processes carried out by the target organisms to detoxify any xenobiotics compound [9]. These are usually degradation processes and it includes oxidation, reduction, hydrolysis or conjugation reactions. Here, the xenobiotic compounds, i.e., propesticides are acted upon by these processes resulting in production of a more toxic material than the original one.

3.3. Activation by symbiont metabolism

Most of the insects harbor symbiotic or parasitic microorganisms in their guts or hemolymph which posses enzymes lacking in them [10]. The various endogenous xenobiotic processes can be brought under control to activate proinsecticidal agents in such organism specific fashion.

3.4. Activation by symbiotic routes

In this path enzymes are not involved. Here, the activation process is not metabolic but results in toxicity because a change in the propesticide occurs in biological milieu.

4. Classification of propesticides

Propesticides can be classified in two ways like based on the number of activation steps involved and based on the type of pest to control [11]. Based on the number of activation steps involved propesticides are classified as single step activation and multiple step activation.

4.1. Single step activation

4.1.1. Juvenogens

- The term juvenogen is used to indicate a new class of the complex chemical compounds which generate products with juvenile hormone activity in response to certain biotic or environmental factors.

- Juvenogen esters when topically applied, the wax-like ester enters the insect body where it is enzymatically hydrolyzed by the carboxylesterase enzymes.
- About two orders of magnitude faster hydrolysis of the juvenogen substrate has been found in the larvae of *Dysdercus*. Here juvenogen has much higher juvenile hormone activity than the hydrolysis alcohol product itself.

4.1.2. Procarbamates and proformamidines

These are derivatives of toxic methyl carbamates insecticides which can be activated to active toxophore either by enzymatic or nonenzymatic. There are also other two possible mechanism of activation of these groups of compounds. These are:

- Acid catalyst hydrolysis of the N-S bond
- Thiol induced thiolysis to form a mixed disulfide and toxic methyl carbamate.

4.1.3. Photoactivated compounds

- Propheromones, xanthene dyes and natural photosensitizers are some types of compounds those functions by photoactivation.
- Xanthene dyes like erythrisin, fluorescin act as phototoxic agents against bacteria and insects.
- Natural photosensitizers like terthienyl and polyacetylines, DNA-damaging agents like dictamine, harmaline are some compounds which act as insecticides.

4.2. Multistep activation

Propesticides requiring more than one metabolic process for activation are known as prepropestides. These are:

4.2.1. Flourocitrate precursors

i. These occur as the toxic principle in legume genera.

ii. One of the first poisons for which the biochemical mode of action was precisely described.

iii. Nissol and Fluemethyl are two commercial product used as acaricides are of relatively lower mammalian toxicity.

4.2.2. Cycloprate

This is activated by two stage of activation process. First is hydrolysis of the cycloprate to free acid followed by formation of carnitine ester [12, 13]. Thus it inhibits the activity of carnitine in transport of fatty acids. Here, the carnitine is an amino acids commonly occurring in the liver and in skeletal muscles that function in the transport of fatty acids across mitochondrial membrane.

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4.2.3. Flouromevalenate

These are potent inhibitors of juvenile hormone production in insects.

5. Based on the type of pest to control

Accordingly propesticides are classified as proinsecticides, proherbicides, profungicides and prorodenticides.

5.1. Proinsecticides

N-Methylcarbamates are another major group of insecticides inhibiting AChE. Although the proinsecticidal features of OP compounds were discovered after their development, proinsecticidal carbamates were designed in Fukuto's laboratory by systematic derivatization to *N*-phosphoryl, *N*-sulfenyl, and related carbamates [14–16]. The biological and toxicological properties of these carbamates could be tailored according to particular use requirements by changing the derivatizing moiety, and thus the physicochemical properties, such as lipophilicity (log P), of the resulting product. The propesticide is activated in the insect by chemical hydrolysis by thiols or other nucleophiles. Nereistoxin is a cyclic disulfide isolated from a marine annelid [17, 18]. It served as the lead compound for the development of the proinsecticides cartap and thiocyclam, both converted into dithiolane acting at the nicotinic acetylcholine receptor of insects. The precocenes, such as precocene 2, on the other hand, were isolated from *Ageratum* sp. plants and found to inhibit the terminal (oxidative) step of JH biosynthesis in the corpora allata, causing precocious development of the insect larva. These anti-juvenile hormones, also called proallatotoxins, are "suicide inhibitors" because the cytochrome P_{450} catalyzed oxidation of the chromene generates epoxide that reacts with neighboring nucleophiles of the enzyme protein, causing massive cellular damage. Diafenthiuron is a thiourea insecticide inhibiting mitochondrial ATPase and acts via its carbodiimide metabolite [19]. The phenylpyrazole fipronil contains a sulfoxide group that can undergo cytochrome P450-catalyzed oxidation in insects to yield a more potent sulfone metabolite. These are meant for controlling insect pest [20]. Some of the proinsecticides along with their active metabolite and activation processes are given in the **Table 1**.

5.2. Rodenticides precursors

Fluoroacetic acid and fluoroacetamide are "lethal precursors" to 2-fluorocitrate. Bitter scilliroside, from the red squill, can be hydrolyzed by glycosidases *in vivo* to scillirosidin, its

Propesticides	Active metabolite	Activation process
Zn_3P_2	PH_3	Hydrolysis/acidolysis
Flouroacetic acid or flouroacetamide	Flourocitric acid	Condensation with oxaloacetate/hydrolysis and condensation with oxaloacetate
Scilliroside	Scillirosidin	Hydrolysis
Bromethalin	—	*N*-Dimethylation

Propesticides	Active metabolite	Activation process
Parathion	Paraoxon	Oxidative disulfuration
Malathion	Malaoxon	Oxidative disulfuration
Disulfoton	Oxydisulfoton	Oxidation
Trichlorfon	Dichlorvos	Rearrangement/dehydrochlorination
Acephate	Methamidophos	Hydrolysis
Carbosulfan	Carbofuran	Hydrolysis
Furathiocarb	Carbofuran	Hydrolysis
Benfuracarb	Carbofuran	Hydrolysis
Thiodicarb	Methomyl	Hydrolysis
Cartap	Nereistoxin	Hydrolysis
Bensultap	Nereistoxin	Hydrolysis/
Thiocyclam	Nereistoxin	Sulfur extrusion/cyclization
Diafenthiuron	—	Oxidative desulfuration
Cycloporate	Cyclopropanecarboxylic acid	Hydrolysis
Chlorfenapyr	—	Oxidation
Sulfluramide	—	Hydrolysis
Fipronil	Fipronil sulfon	Oxidation
Tralomethrin	Deltamethrin	Debromination

Table 1. Active metabolites of proinsecticides and activation processes.

aglycone, which was suggested to be the ultimate rat toxicant. There are a few rodenticides that have either been designed to act as prorodenticides or were found to act as such.

5.3. Profungicides

Profungicides is thiram, or tetramethylthiuram disulfide that is reduced to the corresponding dithiocarbamate, the actual bioactive principle. Dithiocarbamate derivatives of glycerol and other polyols releasing or other related fungicides have also been prepared. The carbonyl group was shown to be reduced stereoselectively into the more potent fungicide triadimenol in fungi and plants, as well as in bacteria. Spirolactone derivatives of the benzoquinone fungicide chloranil provided photostable derivatives that release the parent compound by slow hydrolysis. These are meant for controlling pathogens causing plant diseases. Some of the profungicides along with their active metabolites and activation processes are given in **Table 2**.

5.4. Proherbicides

MCPB and related homologous aryloxyalkanoic acids with an odd number of CH_2 groups provide aryloxyacetic acids, such as (2-methyl-4-chlorophenoxy) acetic acid, whereas

Propesticide	Active metabolite	Activation process
Thiram	*N,N*-dimethylthiocarbamate	Reduction
Dinobuton	Dinoseb	Hydrolysis
Benomyl	Carbendazim and butyl isocyanate	Elimination/hydrolysis
Thiophanate-methyl	Carbendazim	Hydrolysis/cyclization
Triadimefon	Triadimenol	Reduction
Bupirimate	Ethirimol	Hydrolysis
Pyrazaphos		Hydrolysis
Probenazole	Saccharin	Hydrolysis
Acibenzolar-S-methyl	CGA 210007	Hydrolysis

Table 2. Active metabolites of profungicides and activation processes.

Propesticides	Active metabolite	Activation process
MCPB	MCPA	β-oxidation
Naproanilide	2-Naphthoxyacetic acid	Hydrolysis
Chlorazine	Trietazine	Dealkalization
Trietazine	Simazine	Dealkalization
EPTC	EPTC sulfoxide	Oxidation
Triallate	Triallate sulfoxide	Oxidation
Diuron	DCPMU	Oxidative dealkylation
Linuron	DCPMU	Demethoxylation
Methazole	DCPMU	Hydrolysis/reduction
Chlorthiamid	Dichlobenil	Dehydrosulfuration
Metflurazone	Norflurazon	Oxidative dealkylation
Flamprop-methyl	Flamprop	Hydrolysis
Bilanafos	Phosphinothricin	Hydrolysis
2,4-DEP	2,4-D	Hydrolysis/oxidation
Cinmethylin	2-Hydroxy-1,4-cineole	Oxidative dealkylation
Pyrazolynate	Destosyl pyrazolinate	Hydrolysis
Pyridate	CL9673	Hydrolysis
Ethephon	Ethylene	Elimination

Table 3. Active metabolites of proherbicides and activation processes.

those with an even number are degraded to herbicidally inactive phenols [21]. The occurrence of resistance in weeds to triallate has been attributed to reduced sulfoxidation, i.e., bioactivation, rates. The photosynthesis inhibitor *N*,*N*-dimethyl phenylurea diuron is converted into the corresponding *N*-methyl phenylurea DCPMU upon oxidative phosphorylation [22]. Dealkylation of the *N*,*N*,*N*_,*N*_-tetraethyl triazine derivative chlorazine to trietazine then to simazine increases the photosynthesis inhibitory activity by several orders of magnitude. For the rice herbicide thiobencarb (*S*-4-chlorobenzyl diethylthiocarbamate), reductive dehalogenation occurring in soil yields the *S*-benzyl derivative, believed to be responsible for phytotoxicity *in vivo*. These are meant for controlling weeds. Some of the proherbicides along with their active metabolites and activation processes are given in the **Table 3**.

6. Environmental utility of propesticides

Although commonly used structural modifications, carried out during routine structure-activity relationship studies and lead structure optimizations, affect both pharmacokinetics and pharmacodynamics, chemical alterations used in propesticide design are aimed to improve the biological profile by optimizing exclusively the pharmacokinetics of the toxicant. Potential advantages of a propesticide can be summarized as follows:

i. *Alteration of physicochemical properties.*

Altered physicochemical properties leading to improved stability, solubility, or lipophilicity influencing distribution in organism (systemicity).

ii. *Sustaining activity*

Delayed or sustained action due to the slow release of the active agent from its derivatives.

iii. *Increases selectivity*

Increased selectivity, that is, decrease toxicity toward non-target species, due to different metabolism of the parent compound and its derivatives.

7. Conclusion

The structural and metabolic diversity of various pest control chemicals shown above demonstrates the usefulness of the "Trojan horse" principle of chemical formulation. Future research efforts, either capitalizing on known pesticide design practices or discovering new ones based on differences between the xenobiotic metabolisms of various organisms, will lead to new and selective agrochemicals that find and hit the target enzyme or receptor of the pest as "magic bullets."

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