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- A REVIEW

MECHANISTIC APPROACH FOR THE CHEMICAL AND BIO-CHEMICAL ASPECTS OF ORGANOPHOSPHATE PESTICIDES

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ABSTRACT

Organophosphate pesticides are the ester forms of phosphoric acid usually considered as secure for agriculture uses due to their relatively fast degradation rates. Organophosphorus pesticides have been extensively used in the area of agriculture to manage insect or pests of a number of economically important crops. Organophosphate pesticides are well-known as the inhibitor of acetylcholinesterase activity, not in insects only, but can also affect the nervous system of other organisms as well as humans. Organophosphorus pesticides are not restricted to anticholinesterase action, but comprise genotoxicity and teratogenicity. Such severe health consequences signify a requirement for a better understanding of the fate of organophosphates in the environment.

The safe and effective use of pesticides requires knowledge of their mode of action in pests and adverse effects in non-target organisms coupled with an understanding of their metabolic activation and detoxification. Keeping all these things in mind, this review has been written on organophosphorus pesticide's mechanistic pathway and chemistry aspects of toxicity and decomposition pathways during decomposition under different conditions.

Key words: Organophosphate pesticides, Acetylcholinesterase, Decomposition.

History

World Health Organization (WHO) data indicated that more than one million serious accidental and two million suicidal poisonings with insecticides occur worldwide every year and of these approximately 200000 die, mostly in developing countries. There are number of researches regarding pesticides and their toxicity, but two main studies, which initiate us to write about the organophosphate, one in India regarding the monocrotophos and second is the epidemiological analysis in China from 2008 to 2010. In China, sizzling outcomes of

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epidemiological analysis from 2008 to 2010 was analyzed. During the three years, there were 1222 cases reported for pesticide poisoning. Among them, the number of occupational poisoning was 225, out of them 1 case has died, with fatality rate of 0.44%. The number of non-occupational poisoning was 997, out of those, 77 cases has died, and its fatality rate was 7.72%. The incidence of occupational poisoning and non-occupational poisoning accounted for 18.4% and 81.6%, respectively. Male patients were in the preponderance in occupational pesticides poisoning (accounting for 76.4%), female patients in non-occupational poisoning (accounting for 52.1%). The pesticide poisoning chiefly occurred from July to September. Insecticide, generally organophosphates, rank the first in the terms of total poisoning cases caused by pesticides[1]. Other organophosphate insecticide, which got the popularity was monocrotophos in India; proportion of identified pesticides responsible for all deaths reported at MGM hospital, Warangal, In 1997-2001, approximately 54% death case by the use of monocrotophos only has been occurred and among the others maximum were organophosphates[2,3].

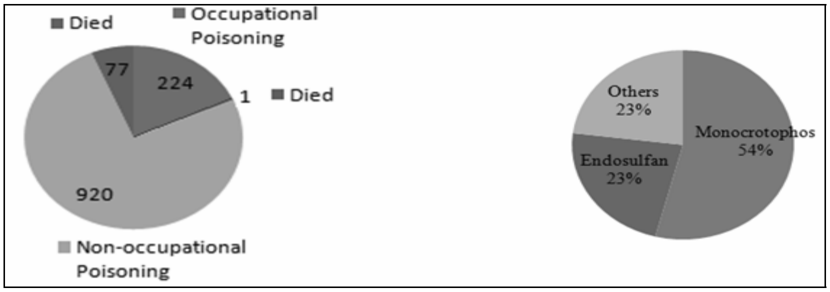


Fig. 1: Pie chart for occupational and non-occupational poisoning in China (Left), deaths reported at MGM hospital (India), Warangal, 1997-2001 (Right)

The above mentioned facts and studies were not restricted to monocrotophos, acephate, and methyl parathion etc. but belongs to all other organophosphates and so, it become the first precedence to know about the chemistry facts especially the basic toxicology, mechanism and their consequences.

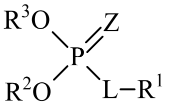
INTRODUCTION

Organophosphate pesticides (OPs) are the ester forms of phosphoric acid usually considered as secure for agriculture uses due to their relatively fast degradation rates[4]. Although the degradation of OPs is a linear function of microbial composition, pH, temperature, structural arrangement etc., OPs inhibit acetylcholinesterase (AChE) activity not only in insects only, but can also affect the nervous system of other organisms as well as humans[5,6]. Literature data illustrated the OPs persistence in soils years after their application[7]. But the reason behind this environmental persistence is not very clear. Pesticides have been transferred to humans through the food chain[8-10] and numbers of environmental and health[11-16] issues have aroused the public concern during last few years. Keeping all these views in mind, we are going to carve a review on OPs with respect to their mechanistic pathways, chemistry aspects.

EXPERIMENTAL

Basic structure of OPs

Organophosphate pesticides derived from phosphorus analog PH_3 having phosphorus as a core nuclei involved in oxidation states (III) and (V). Basically organophosphate is the general name for esters of phosphoric acid.



Z = O or S
R = Me/Et etc.
LR1 = Leaving group,viz.
Alkyl, alkoxy, alkyithio, aryl, hetrocyclic,
Aryloxy, arylthio etc.

Fig. 2: Basic structure of OPs.

Hydrolyzed derivatives of phosphorus formal incorporation of additional oxygen atoms gives phosphinic acid ($O{=}PH_2OH$) and phosphonic (phosphorus) acid [$O{=}PH(OH)_2$]. Notably, these species may tautomerize between P (V) and P (III), that is, $H_2P(O)OH$ to $HP(OH)_2$.[17] Also a tetrahedral structure [$O{=}PH(OH)_2$] is more established than its isomer phosphonic acid, $P(OH)_3$. This form can be stabilized by coordination with some metals[18]. Classes of OPs are viz. phosphates, amidates, thionates, thiolates, phosphonates and phosphinates.

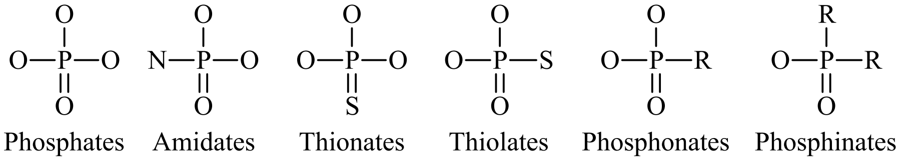


Fig. 3: Different basic species of OPs.

Toxicology

Study indicated that OPs impair the enzymatic pathways involved in metabolism of carbohydrates, fats and protein within cytoplasm, mitochondria, and proxisomes. It is believed that OPs show this effect through inhibition of AChE or affecting target organs directly[17,19]. Acetylcholinesterase (AChE) inhibition is the most illustrious mode of action of the organophosphates. Inhibition occurs through the irreversible binding of organophosphates to the catalytic site of the enzyme. Three basic types with respect to organ system of organophosphate pesticides toxicity are seen i.e. Parasympathetic nervous system, nicotine-receptors system, central nervous system[20]. In all these three, basic mechanism of toxicity is inhibition of acetylcholinestrage due to phosphorylated action of OPs, causing AChE inactivation in an irreversible manner. Enzymatic hydrolysis involves nucleophilic addition and acid-based reactions at the catalytic site of the enzyme that involves a catalytic chord i.e. three amino proteins viz. serine, glutamic acid, and histidine[17,21]. An enzyme-substrate complexation between acetylcholine (ACh) and the enzyme form by electrostatic attractions between the positive charge on the ACh nitrogen and the negative charge in the acidic site. Then the imidazole moiety of the histidine catalyzes acetylation of the serine hydroxyl group; the acetylated enzyme then allows for nucleophilic attack by water to transpire. The deacetylation reaction results in the liberated enzyme and release of inactive choline and acetic acid. Catalytic activity of AChE is very high with a turnover number of >104 s^{-1}.[17,20,21]

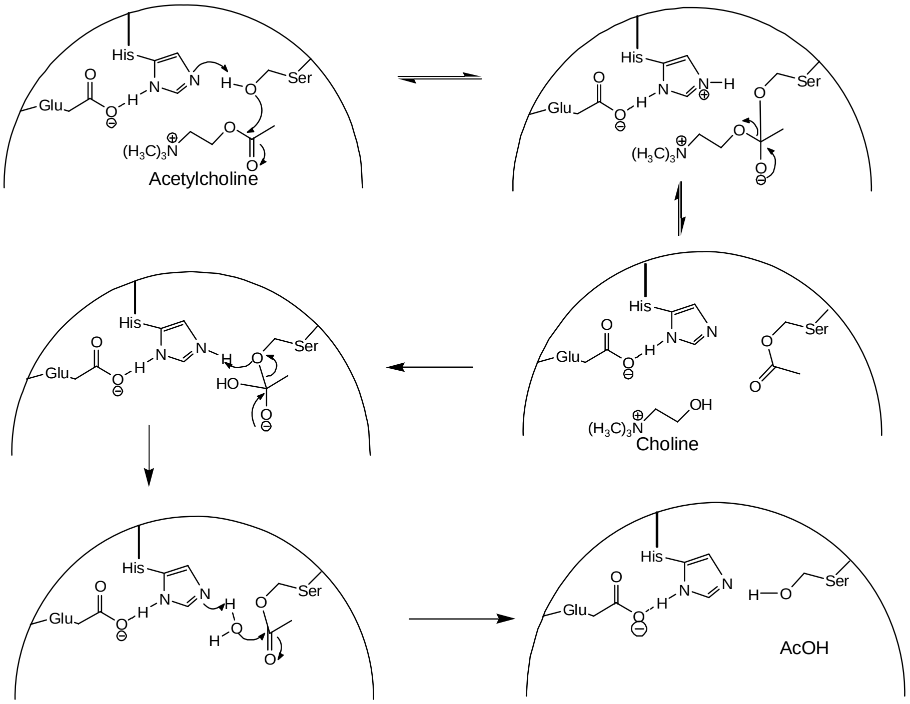


Fig. 4: Acetylcholinesterase hydrolysis of acetylcholine

The mechanism of AChE inhibition with organophosphates is analogous to the reaction of enzyme with ACh, excluding for the reaction in which the leaving group of the organophosphates is lost, so the enzyme becomes phosphorylated instead of acetylated. Phosphorylation is a two-step addition-elimination reaction in which the addition step is rate-determining, while the elimination process is faster. It should be noted that phosphorylation occurs via a trigonal bipyramidal intermediate, whereas in the case of acetylation is anticipated through a tetrahedral intermediate. The irreversibly inhibited phosphorylated enzyme can no longer hydrolyze acetylcholine. This leads to an accumulation of acetylcholine in cholinergic receptors and consequent continuous stimulation of the nerve fiber. Phosphorylated AChE having the stable bonding and forces than acetylated one, but it can undergo a possible secondary process. Among these first one is the reactivation-hydrolysis of phosphorylated enzyme. But the rate of hydrolysis is much slower than in the case of an acetylated enzyme. Another mechanism is the breaking of the PO-C bond the inhibited enzyme known as "aging".[17]

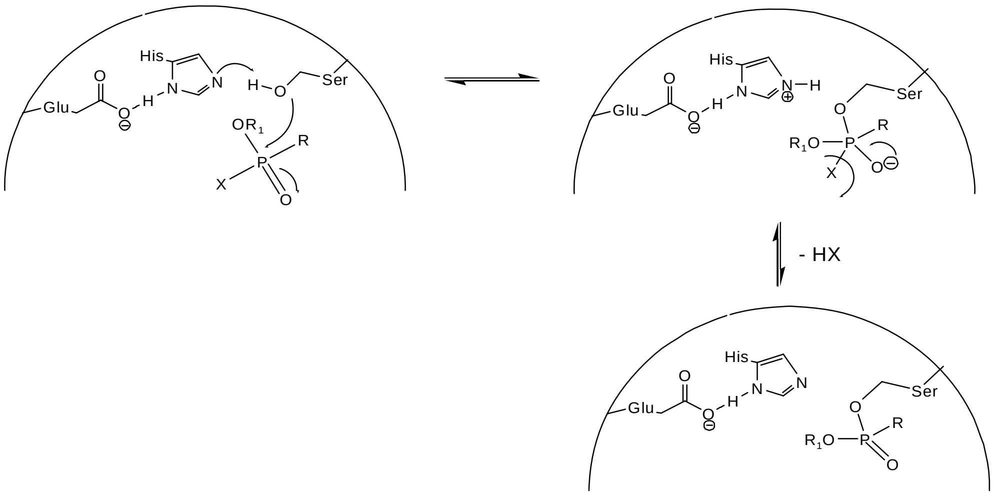


Fig. 5: Inhibition and "Aging" of AChE with OPs.

Our keen analysis indicate that non-enzymatic functions of AChE variants may participate in and be predictive of the relative developmental neurotoxicity of organophosphates, and that the various organophosphates differ in the degree to which they activate this mechanism[22].

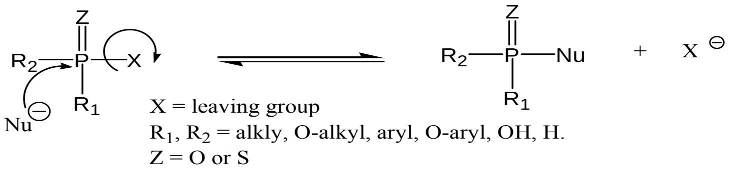
Decomposition methods

Hydrolysis

Alkaline hydrolysis rates are much faster than the corresponding rates under neutral conditions because reaction is initiated by the nucleophilic attack of the hydroxide ion at the phosphorus atom. The reaction depends on the electron deficiency of the phosphorus atom, which may be affected by the electronic properties of substituents on phosphorus. Thus, the hydrolyzability of the esters is increased by the presence of electron-withdrawing groups and is decreased by the presence of electron-releasing groups[23].

The majority of organophosphorus pesticides are phosphorothionate esters, which are generally 2 to 20 times more stable than the corresponding phosphate esters. Sulfur is around 1.4 times less electronegative than oxygen, and therefore, the phosphorus atom of phosphorothionate esters is less electrophilic and consequently less reactive with water or hydroxide ion[23,24]. The rate of hydrolysis for organophosphorus esters is independent of pH in the acidic range (1-5) and they tend to be very stable under such conditions. Conversely, they are much more unstable under alkaline conditions. The hydrolysis rate increases steeply at pH higher than 8 to 12. Since the hydrolysis is primarily catalyzed by hydroxide ion under alkaline conditions, the hydrolysis rate increases around tenfold with each additional pH unit. Rates of hydrolysis are also affected by temperature[17,25]. In the trialkyl phosphates case, both alkaline and acidic conditions hydrolyze via nucleophilic attack on the phosphorus, whereas in neutral solutions, preferential attack on the α-carbon occurs instead of P, only in the case where competing nucleophiles of a “hard base” type does attack occur on the phosphorus “hard acid”.[26,17] Additional mechanisms of hydrolysis not include the amidates, where under basic conditions the nitrogen is free to participate in π-bonding with phosphorus, thus making the center more stable. However, in acidic solutions, the nitrogen is protonated and hydrolysis via amino-P cleavage readily occurs. A phosphorus-carbon bond of phosphonates enhances hydrolysis at high pH because the alkyl group is non-polar and carbon does not participate in π-bonding with phosphorus, placing greater polarity between the P-O bonds. On the other hand, phosphonates and phosphinates are comparatively more stable in acidic conditions than the phosphates[27].

Almost all organophosphates react with water at different pH, which can be considered as a basic method for detoxification and decomposition of OPs[28-30]. Hydrolysis proceeds by phosphorus $S_N{}^2$ nucleophilic attack. The hydrolysis of fenthion, phoxim, dichlorvos, azinphos-methyl, diazinon and parathion-methyl has been studied at different pH and temperatures. It was observed that hydrolysis is a dependent function of pH, temperature, chemical structure and functional groups of a pesticide molecule[31-35]. This reaction most probably gives the non-toxic byproducts.



X = leaving group
R_1, R_2 = alkly, O-alkyl, aryl, O-aryl, OH, H.
Z = O or S

Fig. 6: Hydrolysis proceeds by phosphorus S_N2 nucleophilic reaction

Computational studies on the solvolysis of nerve agents also indicate that the P-O and P-SR bond cleavage processes are kinetically competitive, but the P-SR cleavage pathway is sympathetic over P-OEt bond cleavage by the energy difference of 3.2 Kcal/mol.[36,37]

Peroxide

Basic unit of peroxide is R-O-O-R. Peroxides are basically non-toxic, non-corrosive and having low freezing point and hence, these are considered as attractive moiety for decomposition and detoxification of OPs. Decomposition reaction follows the nucleophilic pathway[38].

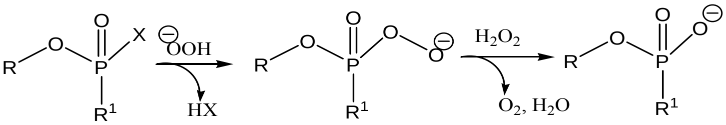


Fig. 7: Nucleophilic pathway of peroxides

This method was considered as more attractive than simple hydrolysis towards OPs[38-42]. As per literature, the rate of detoxification of the malathion, diazinon, parathion and mevinphos is directly proportional to the concentration and pH (> 10).[43-45]

Metal-catalyzed reactions

The mineral-surface-catalyzed hydrolysis and divalent metal ion-catalyzed hydrolysis of thionate (P=S) and oxonate (P=O) organophosphorus pesticides at different pH has been examined in light of three possible catalysis mechanisms : (i) metal ion coordination of the thionate sulphur or oxonate oxygen to enhance the electrophilicity of the phosphorus electrophilic site; (ii) metal ion coordination and induced deprotonation of water to create a reactive nucleophile and (iii) metal ion coordination of the leaving group to facilitate its exit. Results indicate that pH alone cannot be used as a single parameter to predict the hydrolysis of OPs, other parameter such as temperature, metal content and water quality also showed significant effect on the hydrolysis rate[46-53]. As per literature, persistence of pesticides is through chelation/ precipitation/complexation, but it varies from pesticide to pesticide. In most cases, the catalytic enhancement is attributed to metal co-ordination with the substrate. Several different mechanisms of catalysis by metal ions are outlined below: The metal ion acts as an electrophile and co-ordinates the Z atom (either O or S). This has the effect of enhancing the electrophilicity of the phosphorus electrophilic centre making it more prone to attack by OH or H_2O.

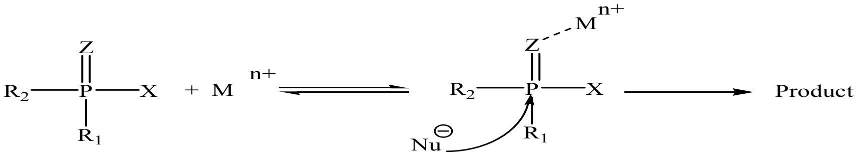


Fig. 8: Metal binding to Z, with resultant increase in the electrophilicity of phosphorus

Metal ion co-ordinates the leaving group, with consequent facilitation of its departure by weakening the O-P bond.

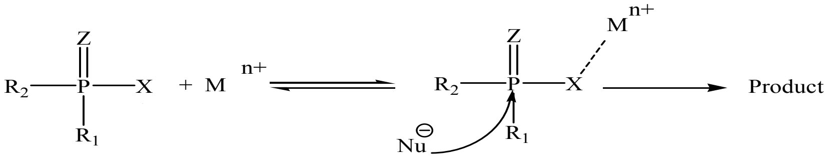


Fig. 9: Metal binding to X, with resultant facilitation of leaving group

A fourth possible mechanism involves metal co-ordination of the nucleophile itself. Such a metal-hydroxide species can subsequently bind the pesticide, with resultant intramolecular –OH attack on the pesticide. This mechanism is more likely to be prevalent in neutral or acidic conditions where the –OH ion concentration is reduced.

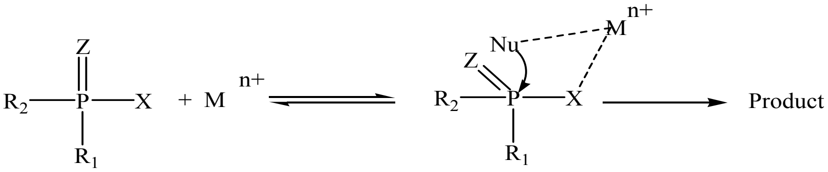


Fig. 10: Intramolecular nucleophilic attack

If two ligands are present in the OP pesticide the second ligand may acts as an auxiliary ligand and enable either (a) the interplay of mechanism 1 and 2, or (b) facilitate the formation of a chelates .

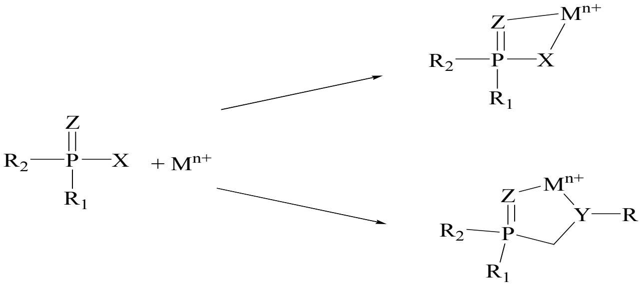


Fig. 11: Metal chelation with OPs

In case of metal catalyzed action, P-O bond cleavage by metal/ metal complexes; the metal-catalyzed hydrolysis literature is widespread, steming from the ubiquity of phosphates in biology, that is, in the backbone of DNA/RNA, which may be cleaved hydrolytically throughout the use of metal complexes. Metals like Cu^{2+}, Co^{2+}, Zn^{2+}, Mg^{2+}, La^{3+}, Sm^{3+}, Eu^{3+}, Yb^{3+}, Mo^{2+}, Zr^{4+}, Ce^{4+}, Hf^{4+} and Th^{4+} were studied for the decomposition of pesticides at pH 8-10 and temperature 25-70°C.[54-56] Metals like Al^{3+}, Cr^{3+}, Co^{2+} and Mn^{2+} were reported in the presence of O_3 involved in PO-R bond cleavage[57-59].

CONCLUSION

Among all the methods of detections, mass spectroscopy based methods are flourished in recent years but there is no development in FTIR and UV based sensing and detection of Ops, which is highlighting a gap in study. Even OPs have the short life time of decomposition but they persist and leach out in soil and environment, which is the matter of huge concern and hence, there is a need to develop the new moieties, which minimize all these risks and hazards. For the future safeguard, there is need to develop antidotes for intoxication with neurotoxic is one of the most important task, not only because their potential use as organophosphorus pesticides, which are very intensively used in agriculture, but also for the treatment of chemical warfare defense agents. There is the need to develop quicker, cheapest, portable methods for agent and pesticides sensing. Nanotechnology and biotechnical approaches may play the wider role for the sensing and decomposition, because till date, these techniques are not developed widely in the field of pesticides. One of the major field, which is almost untouched, that is, decomposition of agents and pesticides in soil because polar nature of OPs in the polar solvents may increase the persistence and leaching and as a result affects the microorganisms of soil due to the high toxicity of OPs, ultimately effects the ecosystem.

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