

Chapter - I: Introduction to Organophosphorus Compounds

Phosphorus was the thirteenth element to be discovered by the German alchemist Hennig Brand in 1669 while distilling urine residues. He obtained a white waxy material that glowed in the dark and burned brilliantly. It was named phosphorus mirabilis ("miraculous bearer of light"). Thus, Brand discovered new element phosphorus. Phosphorus by virtue of its unique electronic configuration $[\text{Ne}] 3s^2 3p^3$, orbital energies and geometry¹ exhibits unique chemistry. It shows multicoordination states P (I to VI) and form well defined classes of multivalence heteroatom compounds with both metallic and non-metallic elements. Interestingly Phosphorus mimics its diagonal relation with carbon and forms several types of Organophosphorus compounds with different functional groups with σ and π single and multiple bonds.² All these Organophosphorus compounds acquire great prominence due to their ubiquitous applications.

Interestingly features of some of the Organophosphorus compounds are presented here to highlight their chemistry and applications.

Organophosphorus Chemistry

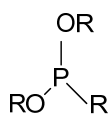
Organophosphorus chemistry is the corresponding science exploring the properties and reactivity of organophosphorus compounds.³



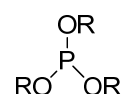
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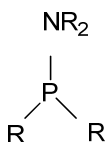
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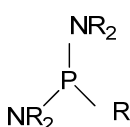
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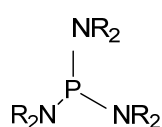
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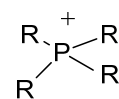
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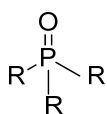
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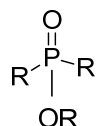
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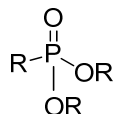
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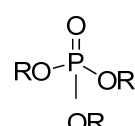
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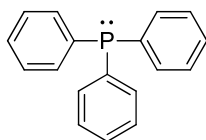
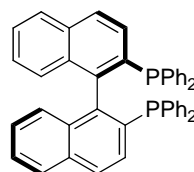


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Common examples of organophosphorus compounds include phosphines **(1)**, phosphinites **(2)**, phosphonites **(3)**, phosphites **(4)**, phosphinousamides **(5)**, diamides **(6)**, triamides **(7)**, phosphonium salts **(8)**, phosphineoxides **(9)**, phosphinates **(10)**, phosphonates **(11)** and phosphates **(12)**.

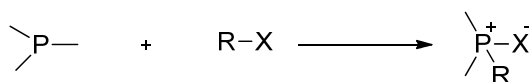
Phosphines:

Phosphines or phosphanes are a group of organophosphorus compounds with the formula R_3P (R = organic derivative). Organophosphines are important in the preparation of catalysts where they complex to various metal ions. Metal complexes derived from a chiral phosphine can catalyze reactions to give chiral, enantioenriched products. Phosphine is mainly consumed as an intermediate in organophosphorus chemistry. In an illustrative reaction, formaldehyde adds in the presence of hydrogen chloride to give tetraakis (hydroxymethyl) phosphonium chloride, which is used in textiles. Related to a PH_3 is the class of organophosphorus compounds commonly called phosphines. These alkyl and aryl derivatives of phosphine are analogous to organic amines. Common examples include triphenylphosphine ($(C_6H_5)_3P$) **(13)** and BINAP **(14)**, both used as ligands in homogeneous catalysis.

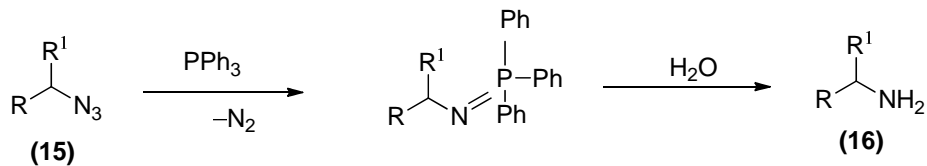
**(13)****(14)**

The main reaction types of phosphines ⁴ are as:

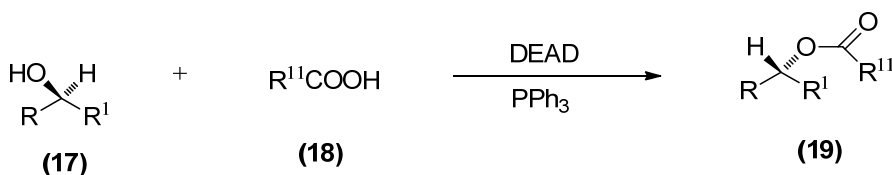
- nucleophiles for instance with alkyl halides to phosphonium salts (**Scheme 1**)
- reducing agents in the Staudinger reduction (**Scheme 2**) converting azides to amines and in the Mitsunobu reaction (**Scheme 3**) converting alcohols into esters. In these processes the phosphine is oxidized to phosphine oxide.



Scheme 1: Nucleophilic attack with alkyl halides



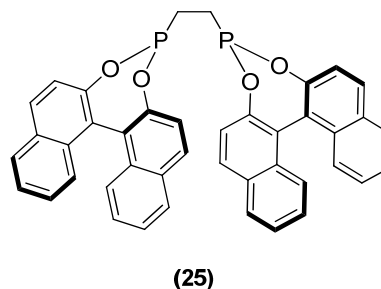
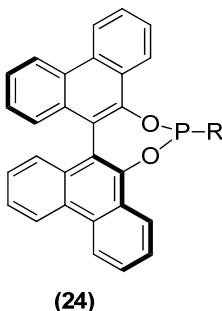
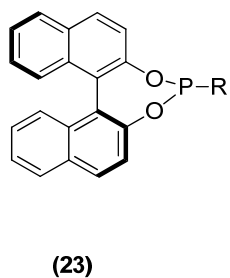
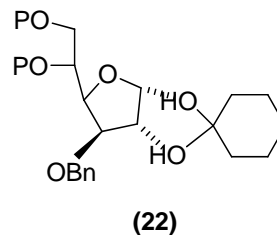
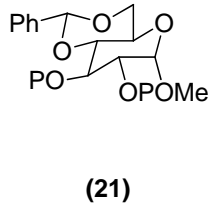
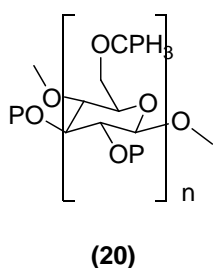
Scheme 2: Staudinger reduction



Scheme 3: Mitsunobu reaction

Phosphinites

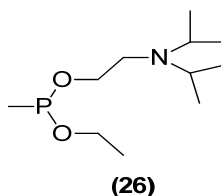
Phosphinites are organophosphorus compounds with the formula $P(OR)_2$. They are used as ligands in homogeneous catalysis and coordination chemistry.⁵



Phosphinites are ligands giving derivatives similar to metal phosphine complexes. They are stronger pi-acceptors than typical phosphine ligands.⁶ Some phosphonite ligands used in Rh-catalyzed hydrogenations are given above.

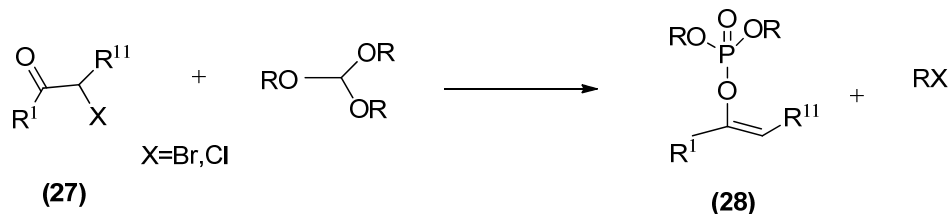
Phosphonites

Phosphonites are organophosphorus compounds with the formula $P(OR)_2R$. They are found in some pesticides and are used as ligands.⁷ Phosphonites can function as ligands in homogeneous catalysis.⁶ One of its derivative, Isopropyl amino ethyl methyl phosphonite (NATO designation QL) (**26**) is a precursor chemical to the nerve agent VX.

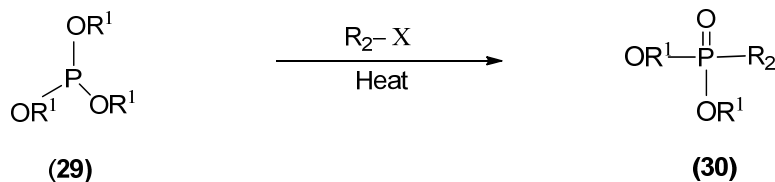


Phosphites

Phosphite esters or phosphites have the general structure $P(OR)_3$ with oxidation state +3. Phosphites are employed in the Perkow reaction⁸ (**Scheme 4**) and the Arbusov reaction⁹ (**Scheme 5**).



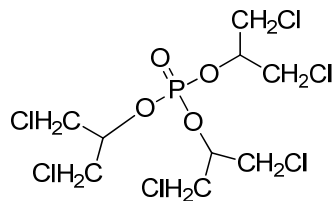
Scheme 4: Perkow reaction



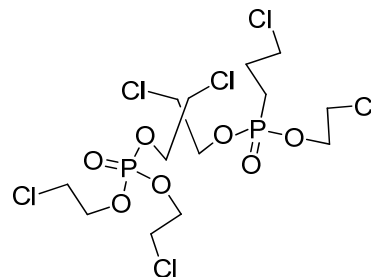
Scheme 5: Arbusov reaction

Phosphate

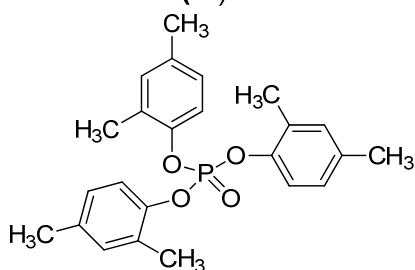
They are derived from phosphoric acid. In organic chemistry, a phosphate, or organophosphate, is an ester of phosphoric acid and alcohol/phenol. Phosphate esters with the general structure $P(=O)(OR)_3$ and oxidation state +5 are of great technological importance as flame retardant agents (**31, 32**)¹⁰ and plasticizers (**33,34**).

Fyrol-FR₂

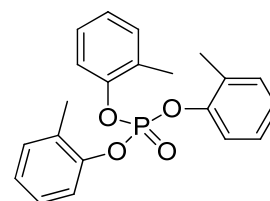
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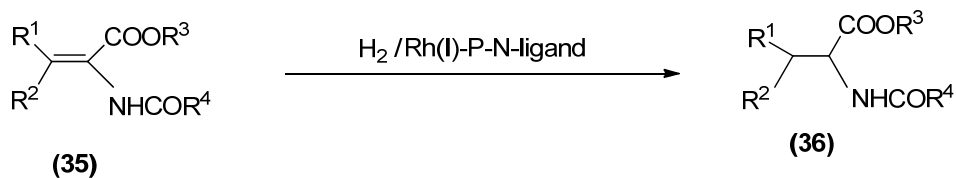
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Phosphinous amides, diamides, triamides

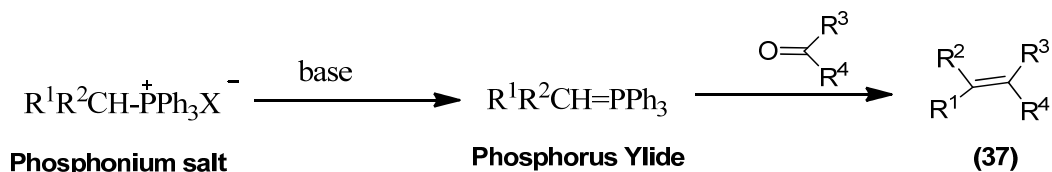
Phosphorus triamides, phosphonousdiamides, and phosphinous amides have found applications as ligands in Rh (I) complexes which have been used in the asymmetric hydrogenation of α -acryloamino acrylic acid derivatives (**Scheme 6**).



Scheme 6: Asymmetric hydrogenation of α -acryloamino acrylic acid derivatives

Phosphonium salt

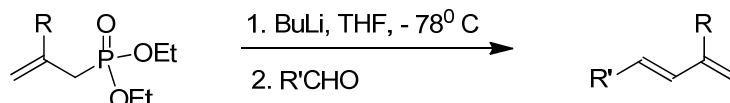
They are quarternary organophosphorus salts ($R_3P^+X^-$). Alkyl triphenyl phosphonium salts are widely used for the preparation of Wittig reagents for the Wittig reaction¹¹ (**Scheme 7**).



Scheme 7: Wittig reaction

Phosphine oxides

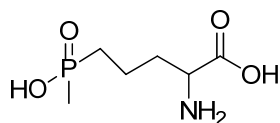
Organophosphorus compounds with the formula OPX_3 ($X = \text{alkyl or aryl}$) are organophosphine oxides. Phosphine oxides are obtained by simple treatment of free phosphine with an oxidizing agent such as H_2O_2 ,¹² $t\text{-BuOOH}$ ¹³ and $m\text{-CPBA}$.¹⁴ Phosphine oxides are typically viewed as useless by-products in the Wittig reaction. They can, however, be usable in certain Wittig-like reactions (**Scheme 8**).



Scheme 8: Wittig-Horner Reaction

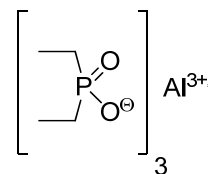
Phosphinates

Phosphinates feature two P–C bonds, with the general formula $R_2P(=O)(OR')$. The Michaelis–Arbuzov reaction is the main method for the synthesis of these compounds. A commercially significant member is the herbicide Glufosinate (**38**). They are found in some pesticides and are used as ligands in homogeneous catalysis⁵ and flame retardants (**39**).



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Herbicide



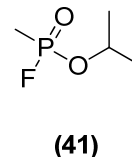
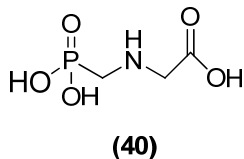
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Flame retardant

Phosphonates

Phosphonates are esters of phosphonic acid and have the general formula $RP(=O)(OR')_2$. They represent an important class of organophosphorus compounds. Their use as reagents in organic synthesis is prevalent and there is a plethora of examples of biologically active compounds possessing the phosphonate moiety. A well-known member being glyphosate (**40**), better known as Round up with the formula

$(\text{HO})_2\text{P}(\text{O})\text{CH}_2\text{NHCH}_2\text{CO}_2\text{H}$, this derivative of glycine is one of the most widely used herbicides. The nerve gas agent sarin (**41**), containing both C–P and F–P bonds, is a phosphonate.



Amongst the above mentioned OPC's, the demand for phosphonates grows steadily at 3% annually as they serve as anthropogenic complexing agents used in numerous technical, an industrial applications, as chelating agents and salt scale inhibitors.

Derivatives of Phosphonates

α -Hydroxyphosphonates

α -Hydroxyphosphonates have acquired an extreme edge both in synthetic chemistry as attractive precursor cum intermediates in development of new synthetic targets¹⁵⁻¹⁷ and in the development of multi-drug agents.¹⁸ They are prominent to act as wide-range enzyme inhibitors for farnesyl protein transferase (FPT)¹⁹, human renin²⁰, human protein tyrosine phosphatase (PTP)²¹, purine nucleoside phosphorylase (PNP)²² and 5-enolpyruvylshikimate-3-phosphate synthase (EPSP)²³.

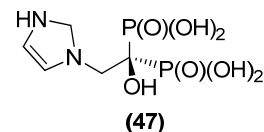
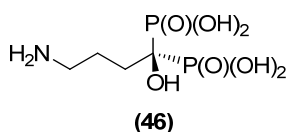
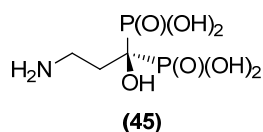
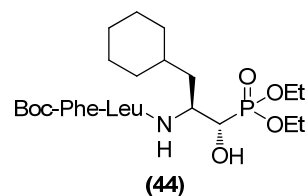
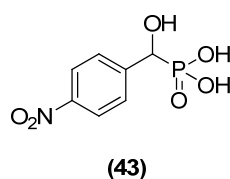
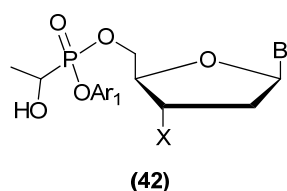


Figure 1: Selected examples of biologically active α -hydroxyphosphonates and α -hydroxyphosphonic acids

The α -hydroxyphosphonates are also potent anti-HIV agents (**42**), potent inhibitor of CD-45 tyrosine phosphatase (**43**) renin inhibitor (**44**) an enzyme inhibitors, their acid derivatives (**45-47**) are also potent anticancer agents (**Figure. 1**). The Pudovik reaction involving addition of dialkylphosphite to carbonyl compounds is a direct method for the construction of new C-P bonds and to generate α -hydroxyphosphonates. The efficiency of this reaction has been improved by the action of catalysts such as enzymatics,²⁴ alkaloids,²⁵ phosphoric acids,²⁶ Lewis acids,²⁷ Al-Li-BINOL complex,²⁸ alumina/ potassium fluoride,²⁹ NH_4VO_3 ³⁰ and polymer/ solid supported base.³¹

α -Aminophosphonates

α -Aminophosphonates and α -aminophosphonic acids are considered as the bio-iso-steric phosphorous analogues of α -amino acids.³² These organophosphorus compounds have drawn the attention of synthetic and medicinal chemists owing to their remarkable biological and pharmacological properties.³³ The major function of these compounds is displayed through metabolic regulation by inhibiting the metalloenzymes which possess amino acids as substrates.³⁴ Moreover, these compounds have been found to be potential antibiotic,³⁵ antimicrobial,³⁶ and antitumor³⁷ agents. They also have several applications in the agricultural industry.³⁸ In view of the immense importance of α -aminophosphonates researchers in recent years have been engrossed in developing new synthetic methodologies for these compounds³⁹.

Fields first proposed and developed a new synthetic route for the synthesis of α -aminophosphonate derivatives in the year 1952 (**Figure.2**) and there by the reaction was named as Kabachnik-Fields reaction⁴⁰.

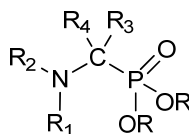


Figure.2: Representative structure of α -Amino phosphonates

The success of his method opened a gateway for the development of the structurally diversified α -aminophosphonates (**48, Figure.3**) *via* a three component condensation reaction of aldehyde, amine and dialkylphosphites.

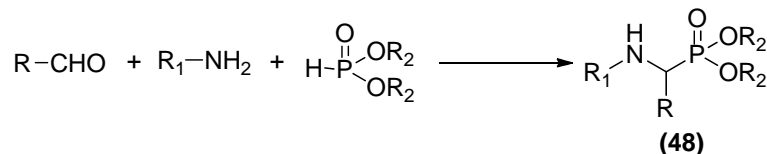


Figure.3: A typical Kabachnik-Fields reaction

Bisphosphonates

Bisphosphonates are a class of drugs that prevent the loss of bone mass and used to treat osteoporosis and similar diseases. They are the most commonly prescribed drugs used to treat osteoporosis.⁴¹ They are called bisphosphonates because they have two phosphonate (PO(OH)₂-C-PO(OH)₂) groups. Methylene bisphosphonates (MBPs) (49) are stable analogues of pyrophosphonates (50), in which the P-O-P is replaced by non-hydrolysable P-C-P groups (Figure.4).

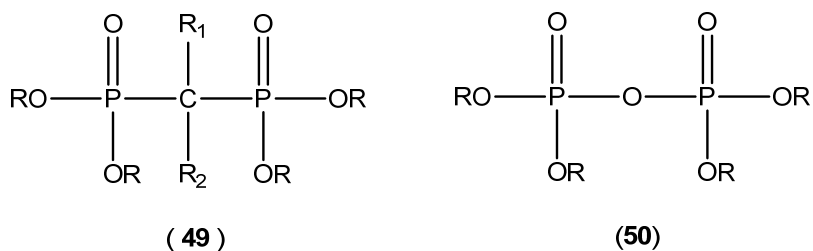
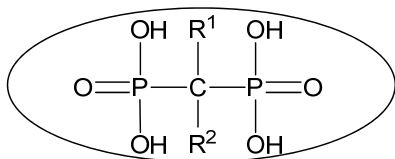


Figure. 4: Structural analogues of bisphosphonates and pyrophosphonates

In clinical medicine, several MBPs such as Etidronate, Clodronate, Pamidronate Alendronate, Risedronate and Ibandronate are established as an effective drug for bone diseases such as Paget's disease, myeloma and bone metastases and for the prevention and treatment of osteoporosis.

Studies of the relationships between bisphosphonates structure and anti-resorptive potency suggest that the ability of MBPs to inhibit bone resorption is dependent on two separate properties of the bisphosphonate (BP) molecule. The two phosphonate groups together with a hydroxyl group at the R¹ position imparts high affinity for bone mineral and acts as a 'bone-hook' allowing rapid and efficient targeting of BPs to bone mineral surfaces. Once localized within bone, the structure and three-dimensional configuration of the R² side chain determine the biological activity on the molecular targets. The understanding of these molecular targets has become much clearer as a result of recent work. The correlation between substituent moieties, their role and potency of BPs is summarized in diagrammatic representation (Figure.5).



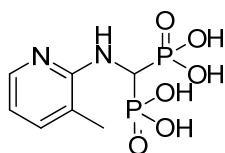
R_1 = OH This group helps to bind to the bone (hydroxyapatite)

R_2 = side chain that determines its anti bone resorption

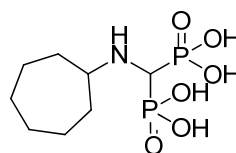
P-C-P = This group acts as "Bone-Hook" and is essential for binding to hydroxyapatite

Figure.5: Structure-activity of BPs

Amino methylene bisphosphonates (AMBPs) are a subclass of MBPs and are currently receiving increased attention of researchers because of their wide range bio-applications. In the previous decade the clinical pharmacology of AMBPs involved treatment of diseases associated with excessive osteoclast-mediated bone resorption such as osteoporosis, hypercalcemia, and Paget's disease. Also they exhibited antiparasitic, antibacterial, and herbicidal activities. A number of AMBPs are also identified as potential low nano molar inhibitors of the enzyme farnesyl pyrophosphate synthase (FPPS), a key regulatory enzyme in the mevalonate pathway. In addition to their activity against FPPS, some AMBPs also inhibit other biosynthesis pathway enzymes, such as squalene synthase, δ' -pyrroline-5-carboxylate reductase, 1-deoxyxylulose-5-phosphate reductoisomerase and *T. cruzi* hexokinase (TcHK). AMBPs are also of interest in the context of cancer therapy since they stimulate human $\gamma\delta$ T cells containing the V γ 2V δ 2 T cell receptor to proliferate and release large amounts of TNF α and IFN γ , leading to potential uses in immunotherapy. Moreover, the high affinity of bisphosphonates for mineralized tissues has led to their application as radio diagnostic tools and bone-targeting moieties for drug and protein delivery with or without a polymeric platform. Some important examples of AMBP drugs with aromatic (NE-97220) or aliphatic (incadronate, YM-175) side chains are given in **Figure.6**.



NE-97220



YM-175

Figure.6: New Amino methylene bisphosphonate drugs

Chromenylphosphonates:

Syntheses of 2-amino-3-cyano-4H-chromen-4-yl-phosphonates are formed through Knoevenagel, Pinner-cyclisation, and phospho-Michael reactions in a one-pot method. In addition, these compounds are analogues of 2-amino-4H-chromenes, and fused chromenes are structural units that possess anti-tumour/cancer⁴² and antiviral⁴³ activity and are used in biodegradable agrochemicals.⁴⁴⁻⁴⁶ There by, the synthesis of 2-amino-3-cyano-4H-chromen-4-ylphosphonates has attracted much attention from chemists.

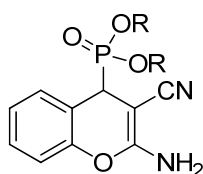


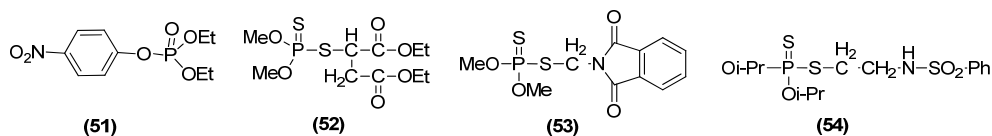
Figure.7:2-amino-3-cyano-4H-chromen-4-ylphosphonates

Uses of organophosphorus compounds:**In Agriculture**

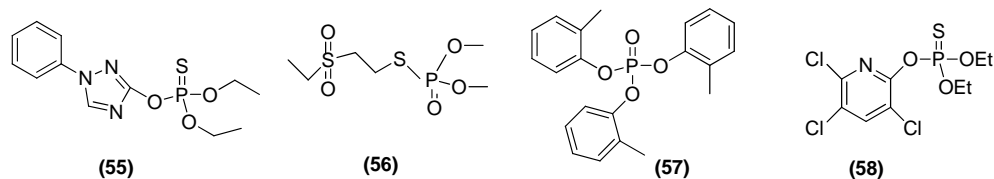
Over the years, many organophosphorus compounds (OPC's) have been made and used in very large quantities in agriculture, not only as pesticides but also later as herbicides. Phosphorus compounds have distinct advantages as pesticides; they are relatively easy to manufacture, biodegrade by hydrolysis, so that the problems of residual toxicity, which is serious with the chlorinated hydrocarbon pesticides, are avoided. The active compounds are normally esters, amides, or thiol derivatives of phosphoric and phosphonic acid.

Parathion (**51**) was one of the first commercially produced insecticides; its toxicity (LD50) is 55 mg/Kg, which is rather low but still requires careful handling and application in the field. It was very popular in 1960s, but after this period the interest in Parathion has greatly declined with the introduction of safer pesticides. Definitely, many compounds are now produced that are relatively harmless to humans yet with excellent toxicity to insects; for example the well-known garden insecticide Malathion (**52**) and Phosmet (**53**) with LD50 up 4000 mg/Kg. On the other hand, the phosphorus

compounds were late entries in the fields of organic herbicides, and to this date only a few compounds have attained major commercial importance. In this regard, Glyphosphate was the first discovered herbicide and is still used. It is known to act by the inhibition of the plant enzyme 5-enolpyruvoyl-shikimate-3-phosphate synthetase, which is involved in the biosynthesis of aromatic aminoacids and other useful aromatic compounds in plants. Many other phosphorus compounds show herbicidal activity, and much research effort is going on in this area. In addition to the phosphorus-containing amino acid derivatives, other structural types are of interest, such as Betasan (**54**).



OPs are marketed by many of the world's major agrochemical companies. Some of the main agricultural products are Hostathion (triazophos) (**55**), Metasystox-R (oxydemeton-methyl) (**56**), Dursban (**57**) and Lorsban (chlorpyrifos) (**58**). OPs have a wide range of pest control applications as contact, systemic and fumigant insecticides.

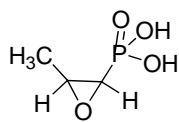


In Medicine

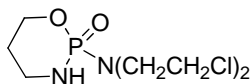
A source of C-P compounds of natural origin was first discovered in 1969⁴⁷ from the products in a fermentation broth of the bacterium *Streptomyces fradiae*. It is a new phosphoric acid derivative that had the antibacterial and antibiotic properties. The compound was named Fosfomycin (**59**) and its discovery was an extremely important event in phosphorus chemistry. Phosphorus compounds had been largely ignored by medicinal chemists seeking new agents against infectious disease. Fosfomycin is active against both Gram-positive Gram-negative bacteria and its effectiveness is comparable to that of the well-known antibiotics Tetracycline. High-level anticancer activity has been found in a large number of other phosphorus compounds of quite different structure and there is much research is going on in this field. Probably the first

organophosphorus compound to receive acclaim as a valuable chemotherapeutic agent is the anticancer drug cyclophosphamide (**60**). Its activity was discovered in 1958 and remains in clinical use even to this day. In the design of anticancer drugs, rationales were done. An obvious one is that an exact phosphonate replica of a known biologically active phosphate could inhibit the process in which the phosphate is involved. The CH₂ group attachment to P which is very similar in size and bond angle with an O atom of a phosphate has great significance in structure-bioactivity relationship. The high stability of P-C bond would block any important natural processes involving hydrolysis of a phosphate ester group. A second rationale is that a phosphonic acid designed to be similar to a naturally occurring carboxylic acid might inhibit the biochemical work of acid. Using these concepts a large amount of phosphonic acids has been synthesized and for them to have useful chemotherapeutic properties.

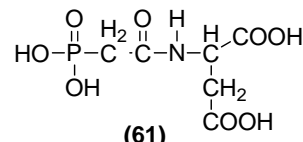
Some examples of the above rationalization are, the PALA (N-phosphonoacetyl-Laspartic acid) (**61**) which is a potent anticancer drug and the Fosinopril (**62**) which has an antihypertensive activity. Phosphorus compounds also have antiviral activity, the first antiviral compound to be discovered had the very simple structure of trisodium phosphono formate. Its activity was discovered in 1978, and is still in clinical use under the name Foscarnet (**63**). It inhibits viral DNA polymerase, and it is a useful agent in the treatment of Herpes and is also active against HIV.



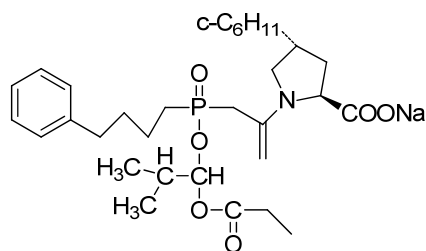
(59)



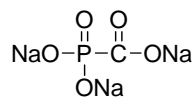
(60)



(61)



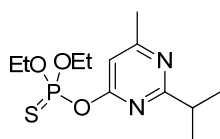
(62)



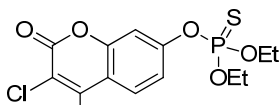
(63)

In Veterinary Medicine

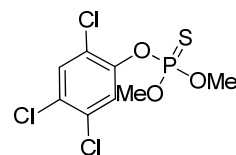
The use of organophosphorus compounds in veterinary medicine is limited, but there is every reason to believe that a wide range of them will become useful in this area.



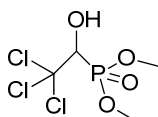
Diazinon
(64)



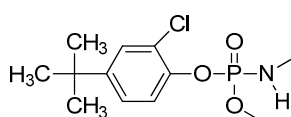
Asuntol
(65)



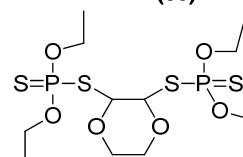
Etrolene
(66)



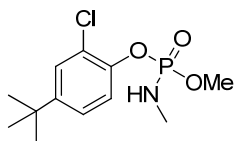
Neguvon
(67)



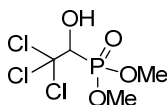
Ruelene
(68)



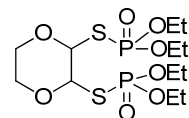
Delnav
(69)



Crufomate
(70)



Trichlorfon
(71)



dioxation
(72)

Compounds **64 to 72** vary greatly in physical and biological properties and especially in stability, solubility and mode of action *in vivo*. Some are contact poisons while others act systemically after absorption from gut, dermis mucous membrane and in some cases after alteration in the body. Some of the OPCs used in veterinary medicine are shown below.

As Dendrimers

Dendrimers are multifunctional, hyper branched and perfectly defined macromolecules, synthesized layer after layer in an iterative manner. Among all types of dendrimers, phosphorus-containing dendrimers that have one phosphorus atom at each branching point, play an important role, with applications ranging from catalysis, engineering materials, and even in nano medicine.

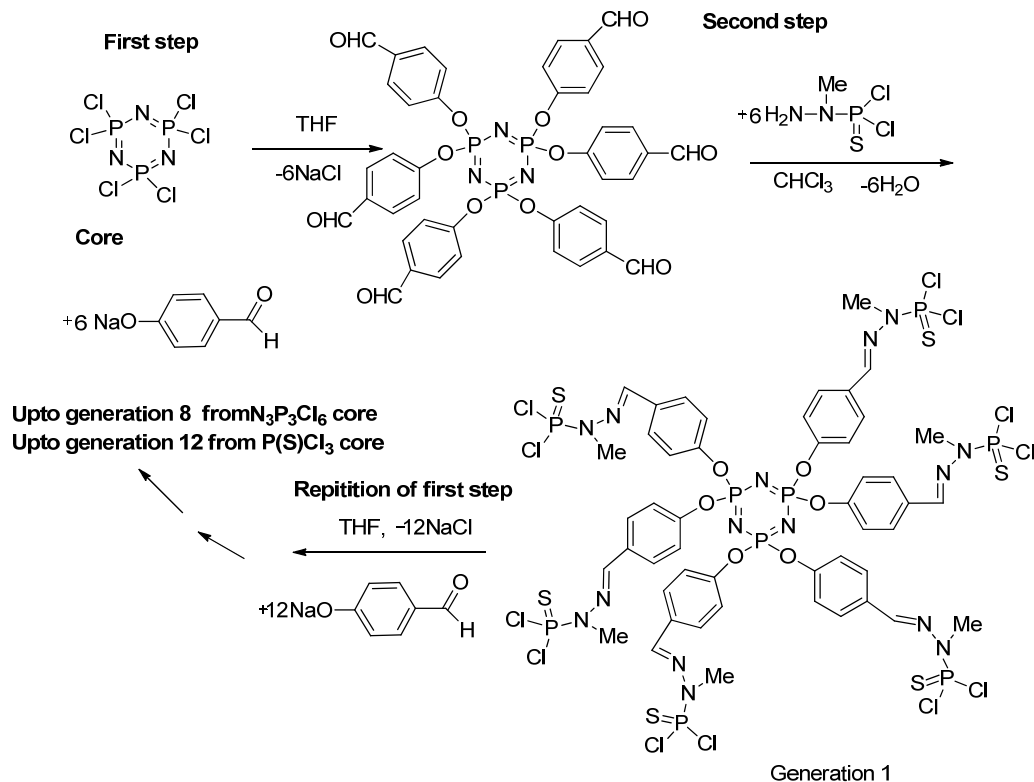
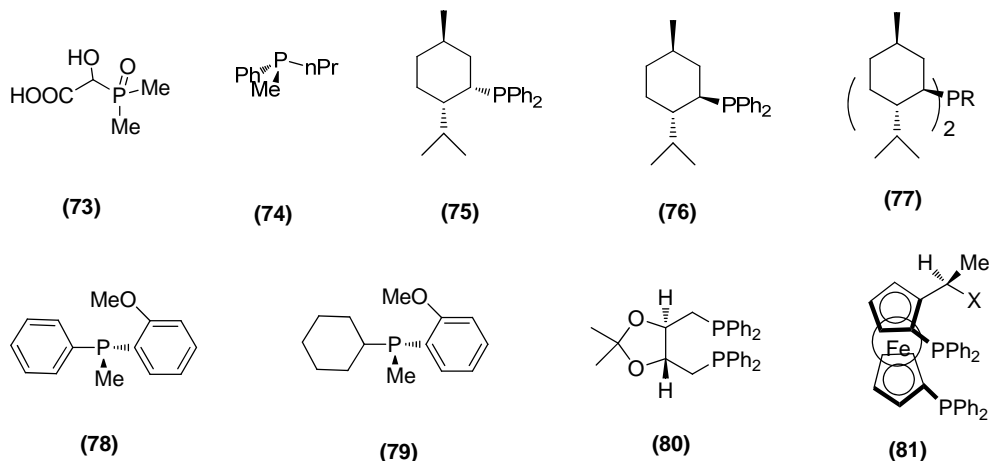


Figure.8: Synthesis of Phosphorus dendrimers

Our first and main method of synthesis of phosphorus dendrimers consists in the repetition of two quantitative reactions, the first step being the nucleophilic substitution of the Cl by 4-hydroxybenzaldehyde in basic conditions. The second step is the condensation of the aldehydes with the dichlorophosphothiohydrazide. This compound is also used in the organic chemistry phosphorus for substitution of Cl of P(S)Cl_3 with methylhydrazine, at low temperature. This second step generates P-Cl_2 functions suitable to perform again substitutions with $\text{HO-C}_6\text{H}_4\text{-CHO}$ (**Figure.8**). This method is very powerful and has been carried out up to generation 8 starting from $\text{N}_3\text{P}_3\text{Cl}_6$, and up to generation of 12 (the highest generation ever synthesized for any type of dendrimers) from P(S)Cl_3 .⁴⁸

As Enzyme Inhibitors and in Catalysis

Many phosphorus compounds have excellent metal chelating properties and this property is important for them to be bio-active by binding with ketol-acid reducto enzyme inhibitors (**73**).

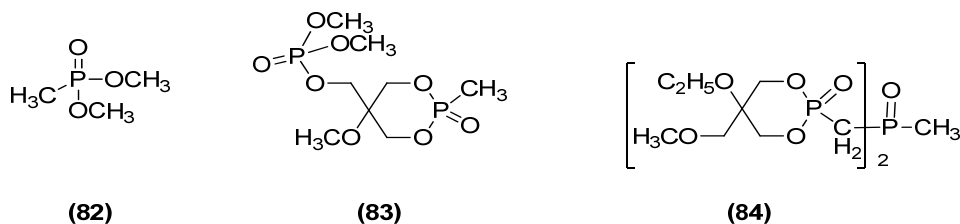


Between various types of enantiomerically pure ligands used for catalytic asymmetric reactions, chiral tertiary phosphines have established their position as the effective ligands for homogeneous transition-metal catalysis. Homogeneous asymmetric hydrogenation started with modest results (ee 15%) in 1968 using chiral monophosphine (MPPP) **(74)** as ligand.⁴⁹ Neomenthylidiphenylphosphine (NMDPP) **(75)** and menthylidiphenylphosphine (MDPP) **(76)** were prepared in 1971 by Morrison et al, gave up to 61% ee in some cases. Knowles et al also published some interesting results in 1972 (ee 90%) with chiral phosphines (PAMP) **(77)** and (CAMP) **(78)**. At the same time alkyldimethylphosphines were used by Wilke, Bogdanovic et al. as ligands of nickel complexes in the catalysis of alkene codimerization and alkene-1, 3-dienes co dimerization. In 1971-1972 they demonstrated that a chelating chiral C₂-symmetric diphosphine (DIOP) **(79)** without asymmetric phosphorus atoms was an excellent enantioselective catalyst (ee 88%). A multitude of chelating diphosphines **(80)** C₁ or C₂-symmetry are presently known; some of them are patented because of industrial applications. One of the most effective chiral biphosphine ligands is BINAP which has exhibited its high enantioselectivity in several asymmetric reactions including rhodium or ruthenium catalyzed hydrogenation. Another important class of chelating biphosphine ligand is ferrocenyl biphosphine BPPF-X **(81)** which had been demonstrated to be effective for palladium-catalyzed allylic substitution reactions, gold- or silver-catalyzed aldol reactions, and so on.

Other uses

Organophosphorus compounds, have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators.⁵⁰ They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma.⁵¹ In academic research organophosphorus compounds find important application in organic synthesis (Wittig, Mitsunobu, Staudinger, organocatalysis etc.)⁵² The use of Organophosphorus compounds as achiral or chiral ligands for transition metal catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production.⁵³

Furthermore, organophosphorus compound can be used as flame retardants for fabrics and plastic plasticizing and stabilizing agents in the plastics industry. Dimethyl methyl phosphonate (DMMP) (**82**) has 25% of phosphorus content and it is the highest phosphorus containing organophosphorus flame retardant. Antiblaze 19 (**83**) and the compound Antiblaze 1045 (**84**) are useful as flame retardants for polyester fabric.



In detergents OPCs are used as a combination of chelating agent, scale inhibitor, and bleach stabilizer. They are also used as selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors. The materials Zn-AMP, Zn-HDTMP, Ca-PBTC (**Figure.9**) act as good anticorrosion agents.

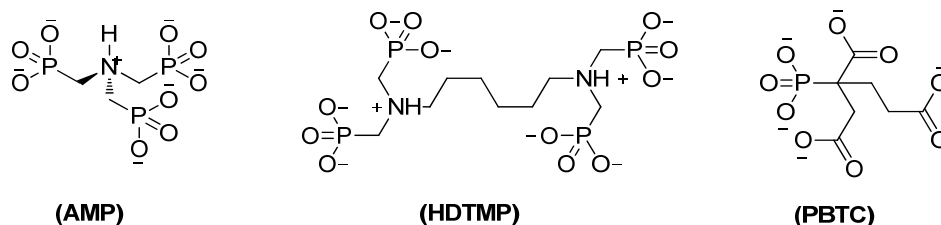


Figure.9: Anticorrosion agents

In view of interesting chemistry a wide applications of OPC, a detailed study on the synthesis and biological evaluation of some new classes of OPCs has been undertaken.

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