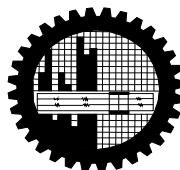


SYNTHESIS OF FUNCTIONALIZED ORGANOPHOSPHORUS COMPOUNDS OF BIOLOGICAL IMPORTANCE



**A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT
FOR THE DEGREE OF MASTER OF PHILOSOPHY (M. PHIL.) IN CHEMISTRY**

SUBMITTED

BY

MOHAMMAD ANWAR-UL-AZIM

ROLL NO. 040803103P

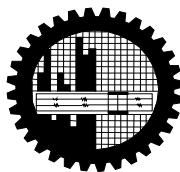
REGISTRATION NO. 040803103P

SESSION: April, 2008

**ORGANIC RESARCH LABORATORY
DEPARTMENT OF CHEMISTRY
BANGLADESH UNIVERSITY OF ENGINERING AND TECHNOLGY (BUET)
DHAKA-1000, BANGLADESH**

SEPTEMBER, 2011

Dedicated
TO
My Parents



Certification of Thesis

A Thesis on

SYNTHESIS OF FUNCTIONALIZED ORGANOPHOSPHORUS
COMPOUNDS OF BIOLOGICAL IMPORTANCE

BY

Mohammad Anwar-ul-Azim

Roll No: 040803103 P, Session: April/2008 has been accepted as satisfactory in partial fulfillment of the requirements for the degree of Masters of Philosophy (M. Phil.) in Chemistry on September 20, 2011.

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This thesis work has been done by the candidate himself and does not contain any material extracted from elsewhere or from a work published by anybody else. The work for this thesis has not been presented elsewhere by the author for any degree or diploma.

September 20, 2011

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Author

(Mohammad Anwar-Ul-Azim)

Chapter 1



INTRODUCTION

Chapter 2



EXPERIMENTAL

Chapter 3



RESULT & DISCUSSION



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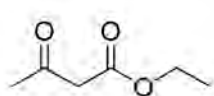


SUMMARY

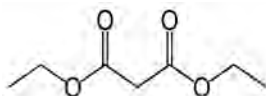
SUMMARY

Organophosphorus compounds have tremendous importance in the field of food technology, animal foodstuff, pesticides, medical compounds, synthetic polymers, fire retardants and natural products. Nucleophilic Substitutions at the carbon centre is very important topic in organic chemistry. Considerable amount of work have been carried on nucleophilic substitution at the carbon centre but much less is known about nucleophilic substitution at the phosphorus centre. Nucleophilic substitution at the phosphorus centre is very important topic in in organophosphorus chemistry. The nucleophilic substitution at the carbon centre is well established but the mechanism of nucleophilic substitution at phosphorus is not well established. It has grown great interest to study nucleophilic substitutions at phosphorus centre.. In view of the extensive use of organophosphorus compounds we synthesize phosphine oxide from active methylene compounds.

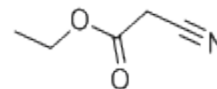
In this thesis work, the following six active methylene compounds were used as starting materials for the synthesis of phosphine oxide:



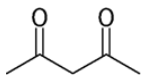
Ethylacetoacetate



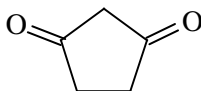
Diethyl malonate



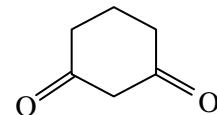
Ethylcyanoacetate



Acetyl acetone



1, 3-Cyclopentanedione



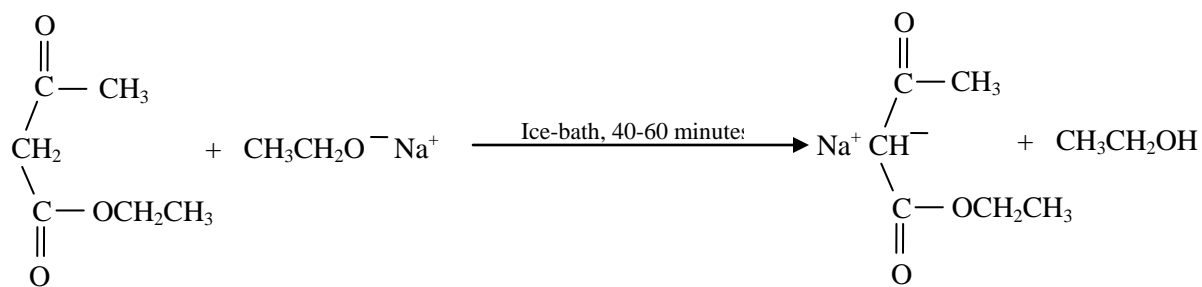
1, 3-Cyclohexanedione

Synthesis of phosphine oxide by using active methylene compounds as starting materials involve the following steps:

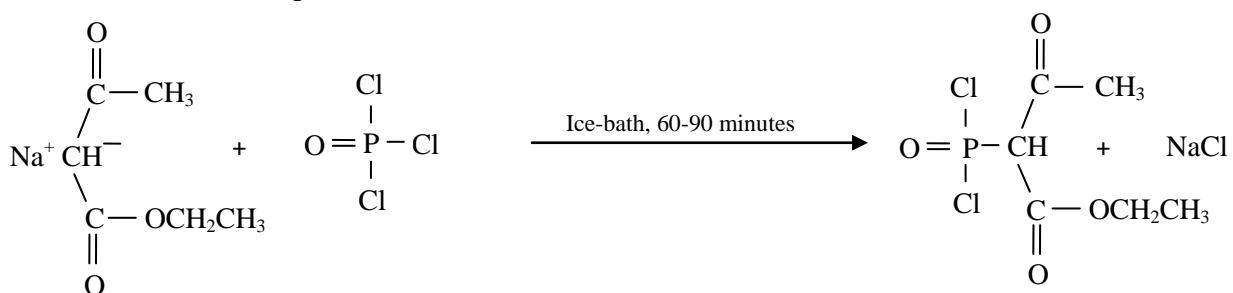
Step 1: Sodium metal reacts with absolute ethanol to sodium ethoxide at room temperature.



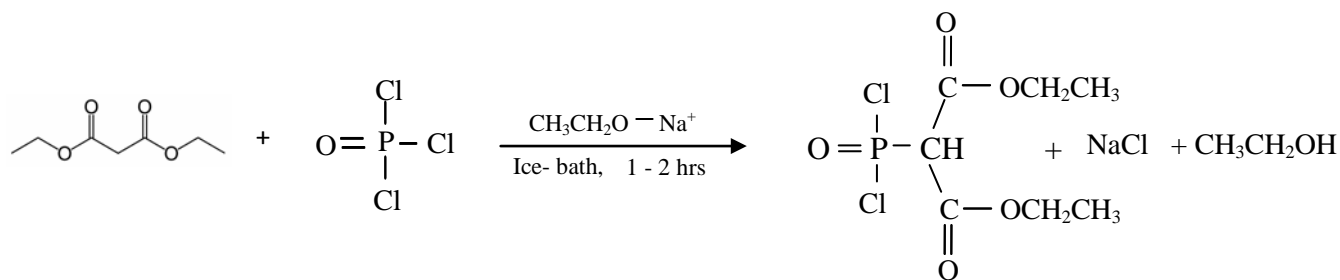
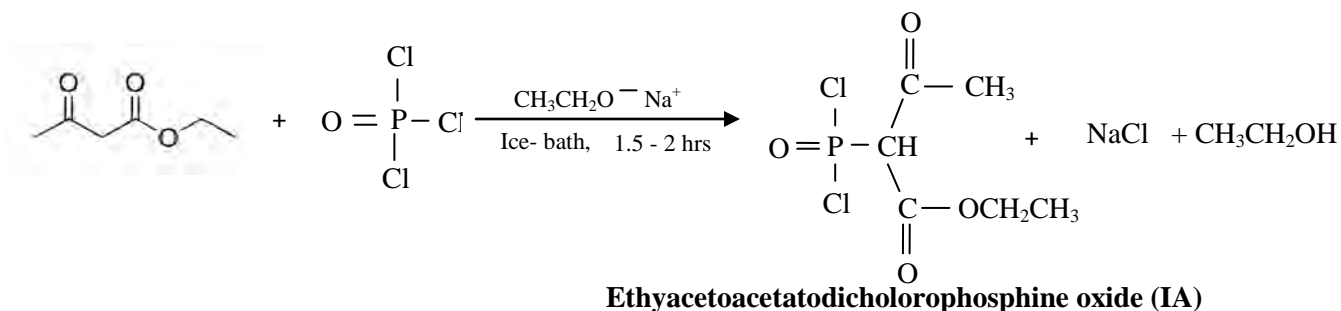
Step 2: The active methylene compounds react with sodium ethoxide to form sodium salt of active methylene compounds at ice-bath.

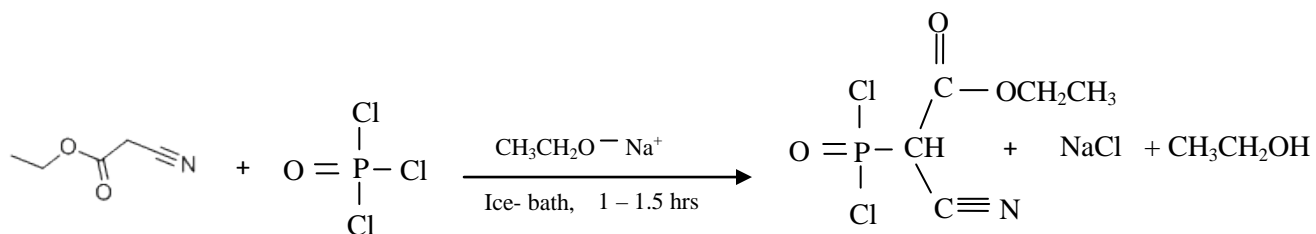


Step 3: Sodium salt of active methylene compounds then reacts with phosphoryl chloride at ice-bath to form desired compounds.

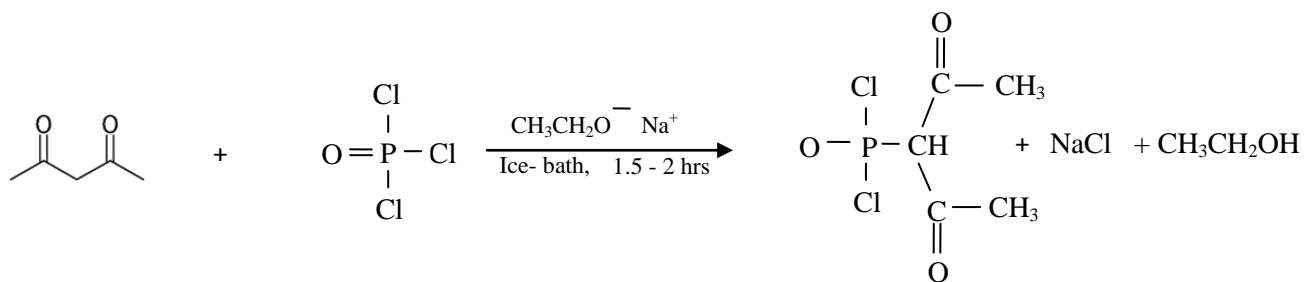


The overall reactions of different active methylene compounds with phosphoryl chloride to form different phosphine oxide are as follows:

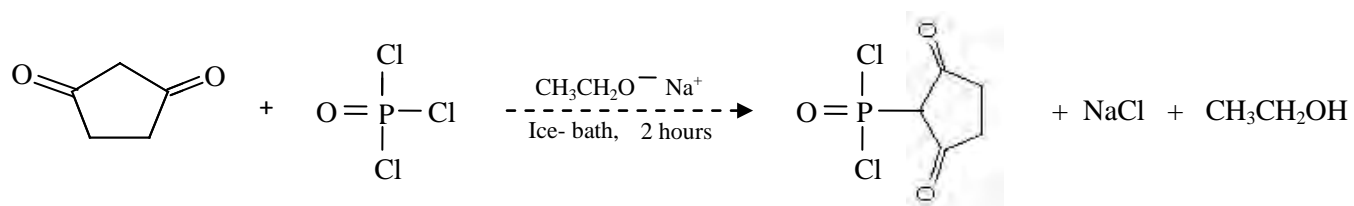




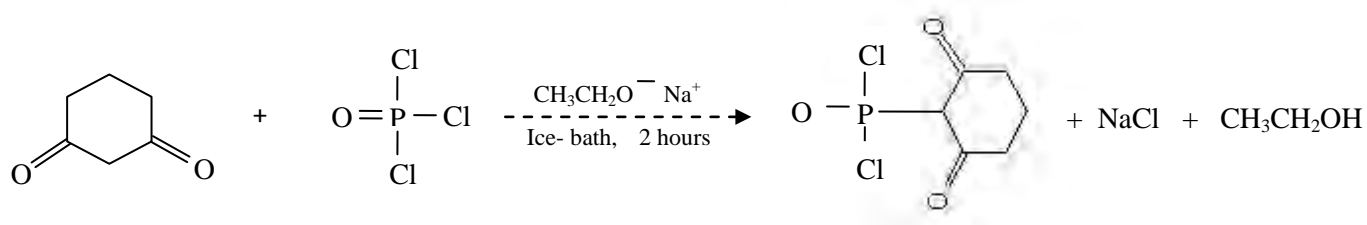
Ethylcyanoacetatodichlorophosphine oxide (3A)



Acetylacetonatodichlorophosphine oxide (4A)



1,3-cyclopentanedionydichlorophosphine oxide (5A)
(No reaction Occurred)



1,3-cyclohexanedionydichlorophosphine oxide (6A)
(No reaction Occurred)

All the synthesized compounds were characterized by using analytic data obtained from melting point, IR and GC-MS spectroscopy.

Table 1: Synthesis of organophosphorus compounds.

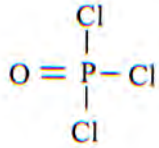
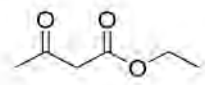
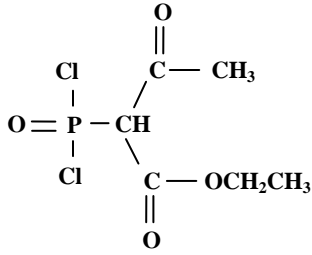
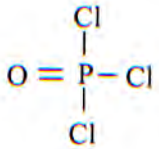
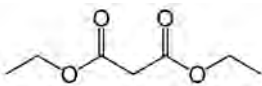
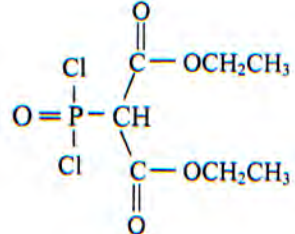
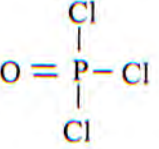
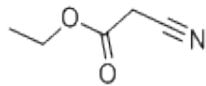
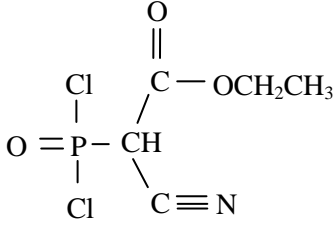
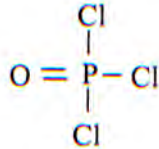
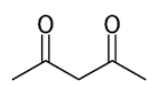
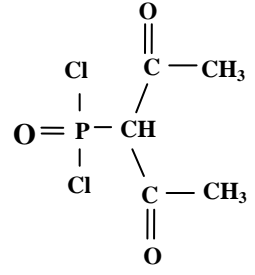
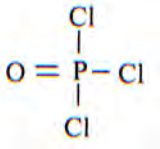
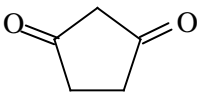
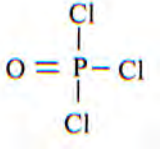
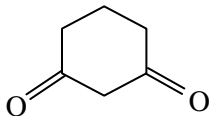
Sl No	Starting Materials	Product	% of Yield	
1	 Phosphoryl Chloride	 Ethylacetoacetate	 Ethylacetoacetatodichlorophosphine oxide (1A)	66.66%
2	 Phosphoryl Chloride	 Diethyl malonate	 Diethylmalonatodichlorophosphine oxide (2A)	64.81%
3	 Phosphoryl Chloride	 Ethylcyanoacetate	 Ethylcyanoacetatodichlorophosphine oxide (3A)	67.22%
4	 Phosphoryl Chloride	 Acetyl acetone	 Acetylacetonatodichlorophosphine oxide (4A)	65.36%

Table 1: Synthesis of organophosphorus compounds.

Sl No	Starting Materials		Product	% of Yield
5	 Phosphoryl Chloride	 1, 3-Cyclopentanedione	No reaction Occurred	-----
6	 Phosphoryl Chloride	 1, 3-Cyclohexanedione	No reaction Occurred	-----

AIM OF THE RESEARCH PROJECT

Organophosphorus compounds have tremendous importance in the field of food technology, animal foodstuff, pesticides, medical compounds, synthetic polymers, fire retardants and natural products. Organophosphorus compounds have many fold uses as medicinal compounds. Despite their diverse structures, Organophosphorus compounds owe their activity to their capacity to phosphorylate and to inhibit the action of cholinesterase, although in some instances the inhibitors of other viral enzyme are believed to be involved. Phosphonomycin, phosphonoformic acid (PFA) and phosphonoacetic acid (PAA) are found to have antiviral properties. Some inorganic phosphorus salts have long been established medicinal uses. A number of well known phosphate salts of organic drugs are prescribed as medicine. This is because, the phosphate generally causes less disturbance to physiological pH, it may have more suitable solubility, or merely because it is the salt most conveniently prepared and purified. Etane -1 – hydroxy – 1, 1 – diphosphonate (EHDP) and its related compounds are used in the treatment of bone diseases. A number of phosphorothioates show antiradiation activity and are excellent radio protective agents. Organophosphorus compounds can also be used as flame retardants for fabric and plastic, plasticizing and stabilizing agents in the plastic industries, additive in the petroleum products and corrosion inhibitors. The intimate involvement of organophosphates in living process is now all recognized and modern biochemistry is dominated by it such as ATP and DNA.

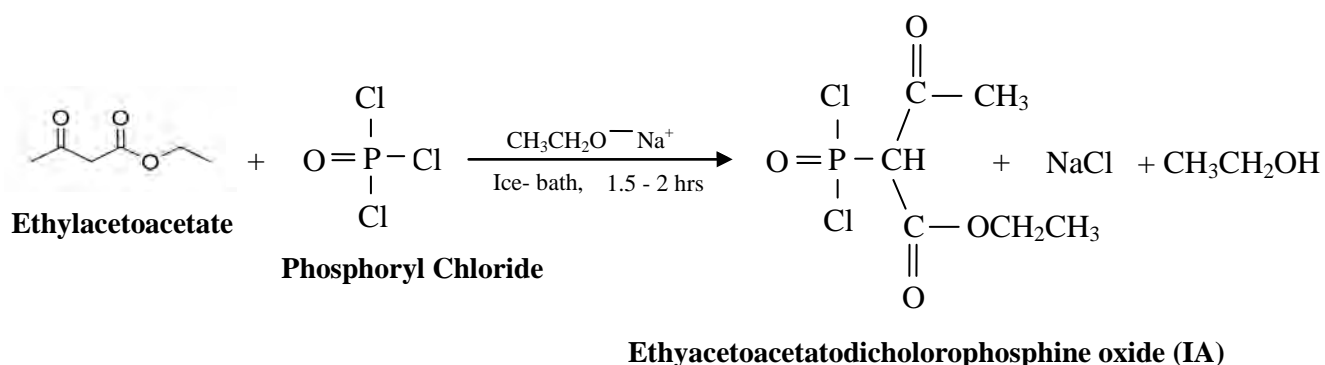
Metrifonate, is an alkoxy derivative of phosphonyl oxychloride is used for the treatment of urinary tract infections and diethylstilbestrols are used in the treatment of prostatic carcinoma. Phosphoroacetic acid is active against Herpes and Marek's disease and phosphoromycin shows anti-bilherzozic and anti – lprosy properties as well as functioning as broad spectrum antibiotic. Walker and Gait reported the broad spectrum antibacterial activity of ribavirin and difficidin. In recent years an important advance has been made in the discovery of the carcinostatic properties cyclophormamide and its derivatives. Schaffer reported the potential antibacterial activity of acyclovir and azidothymidine as amino phosphorus compounds. Small difference of structure often corresponding to larger difference in biological activity. Recently Lee et all synthesized some organophosphates compounds forming phosphorus oxychloride and proposed a mechanism from concerted process to step wise process.

Therefore, organophosphorus compounds composed of active functionalities have been advancement with importance in organic and bio-organic chemistry. From the literature survey, it has drawn a great interest to synthesize organophosphorus compounds having different functionalities which might have biological activity.

Therefore, the proposed research project is undertaken with the following objectives:

- a) To purify the starting materials and solvents.
- b) To synthesized the functionalized organophosphonyl derivatives.
- c) To establish the structure of the synthesized products by various physical methods and spectroscopic evidences such as IR, ^1H NMR, ^{13}C NMR, ^3P NMR, UV.
- d) To study the biological activity of the synthesized products if possible.

2.1 Synthesis of Ethylacetoacetatodichlorophosphine oxide.



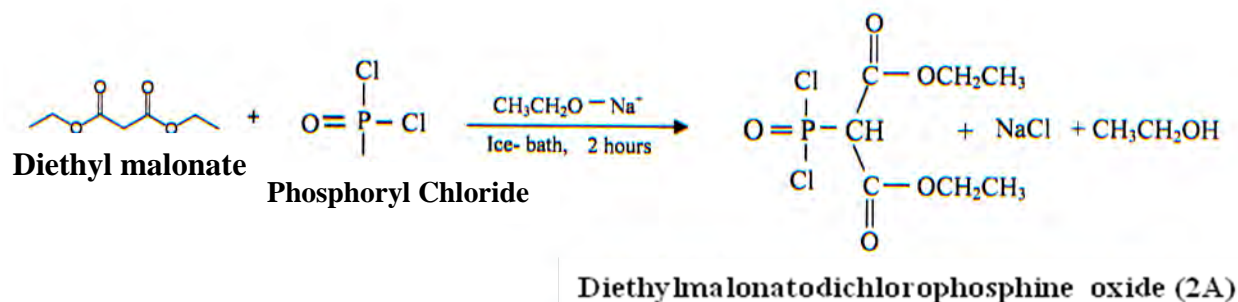
Procedure:

Sodium metal (2.5M, 0.37375 gm) was added to a reaction flask containing 10 ml of absolute ethanol and was stirred for 20 minutes at room temperature. The flask was then placed in an ice bath and then ethylacetoacetate (2.5 M, 2.11 gm) was added to the same flask and stirring was continued for further one hour. A solution of phosphoryl chloride (0.0065 M, 1.00 gm) in ethanol was added drop wise to the reaction mixture and stirred for one and half hour at the same condition. The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was then filtered and evaporated to dryness by a rotary evaporator. The resultant solid mass was then transferred to a mixture of ethyl acetate and water (1:1). The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4 . The crude product was then purified with column chromatography. A white solid product **1A**, melting point 87°C , having yield of 66.66% was obtained. The product was found to be homogenous on TLC plate, R_f value 0.20 (Ethylacetate: n-Hexane = 1:4).

IR (KBr) : $\bullet_{\text{max}}(\text{cm}^{-1})$ 2930 (C-H, $\text{CH}_3 - \text{C} = \text{O}$), 2923.9 (C-H, $\text{CH}_2 - \text{CH}_3$), 2844.8 (C-H, $\text{OCH}_2 - \text{CH}_3$), 1720-1630 (P = O), (CO - OC_2H_5), (CO - CH_3), 1180 (P- Cl), 1170.7 (P- Cl), 1143.7 (P- C).

GC-MS : m/z 246 (Molecular ion peak).

2.2 Synthesis of the Diethylmalonatodichlorophosphine oxide.



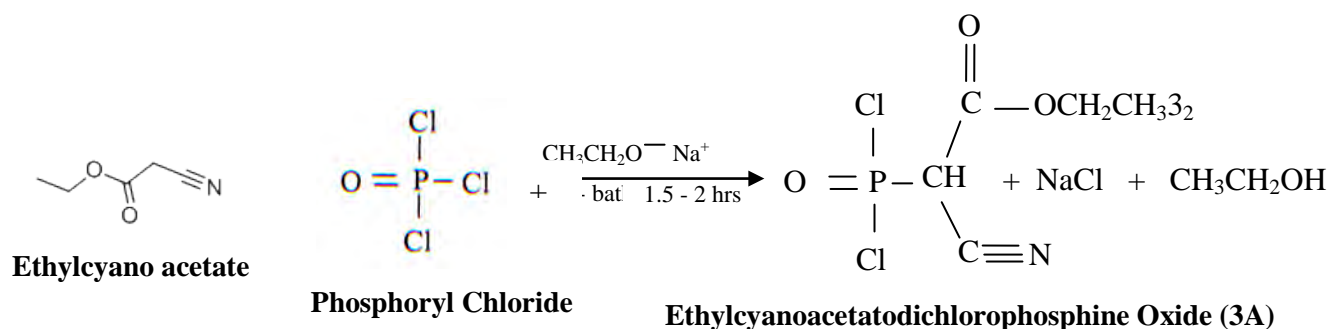
Procedure:

Sodium metal (2.5M, 0.37375 gm) was added to a reaction flask containing 10 ml of absolute ethanol and was stirred for 20 minutes at room temperature. The flask was then placed in an ice bath and then diethylmalonate (2.5 M, 2.60 gm) was added to the same flask and stirring was continued for further one hour. A solution of phosphoryl chloride (0.0065 M, 1.00 gm) in ethanol was added drop wise to the reaction mixture and stirred for one and half hour at the same condition. The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was then filtered and evaporated to dryness by a rotary evaporator. The resultant solid mass was then transferred to a mixture of ethyl acetate and water (1:1). The organic layer was separated, washed with brine and dried over anhydrous Na₂SO₄. The crude product (1.62 gm) was then purified with column chromatography. A yellowish liquid product 2A, melting point having a yield of 64.81% obtained. The product was found to be homogenous on TLC plate, R_f value 0.63, (Eathylacetate: n-Hexane = 2:8).

IR (KBr) : •_{max}(cm⁻¹) 2970 (C-H,OCH₂-CH₃), 2921(C-H, OCH₂-CH₃), 2850 (C-H, OCH₂-CH₃), 1725-1635.5 (C = O), (C = O), (P = O), 1450 (P- Cl), 1371 (P- Cl), 1371.13 (P- C).

GC-MS : m/z 264 (Molecular ion peak).

2.3 Synthesis of Ethylcyanoacetatodichlorophosphine oxide.



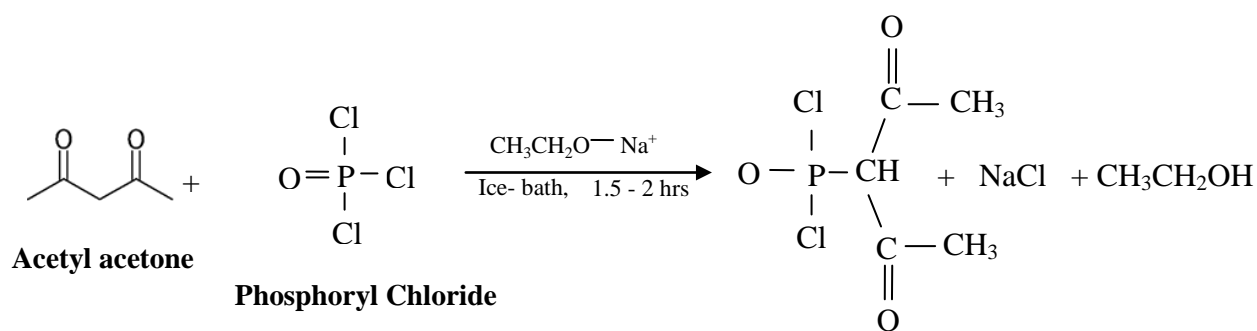
Procedure:

Sodium metal (2.5M, 0.37375 gm) was added to a reaction flask containing 10 ml of absolute ethanol and was stirred for 20 minutes at room temperature. The flask was then placed in an ice bath and then ethylcyanoacetate (2.5 M, 1.836 gm) was added to the same flask and stirring was continued for further one hour. A solution of phosphoryl chloride (0.0065 M, 1.00 gm) in ethanol was added drop wise to the reaction mixture and stirred for one and half hour at the same condition. The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was then filtered and evaporated to dryness by a rotary evaporator. The resultant solid mass was then transferred to a mixture of ethyl acetate and water (ethyl acetate: water = 1:1). The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4 . The crude product (2.38 gm) was then purified with column chromatography. A gray solid product (3A), melting point $105^\circ\text{C} - 106^\circ\text{C}$ having yield of 67.22% was obtained. The product was found to be homogenous on TLC plate, R_f value 0.81, (Eathylacetate: n-Hexane = 4:6).

IR (KBr) : $\bullet_{\text{max}}(\text{cm}^{-1})$ 2997.8 (C-H, $\text{OCH}_2\text{-CH}_3$), 2975(C-H, CH_3), 2970 (C-H, $\equiv \text{N}$), 2237.3 ($\equiv \text{N}$), 1656.7(C = O), 1651 (P = O), 1446.5 (P- Cl), 1406 (P- Cl), 1384.8 (P- C).

GC-MS : m/z 229 (Molecular ion peak).

2.4 Synthesis of Acetylacetonatodichlorophosphine oxide



Acetylacetonatodichlorophosphine oxide (4A)

Procedure:

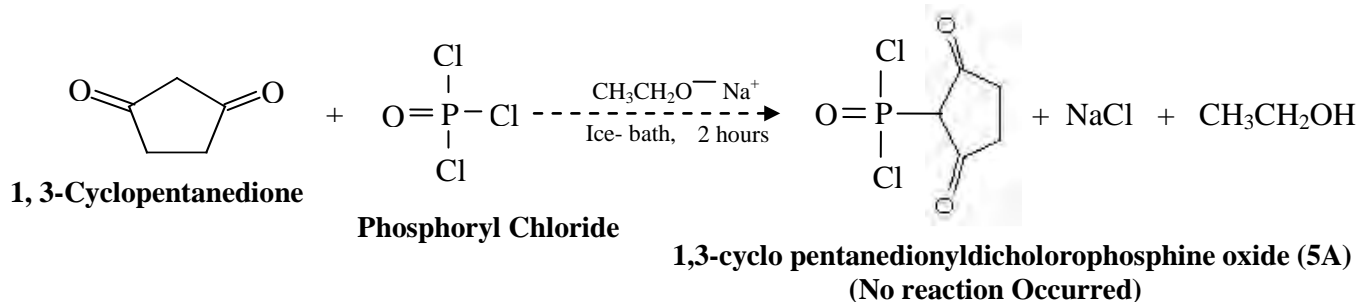
Sodium metal (2.5M, 0.37375 gm) was added to a reaction flask containing 10 ml of absolute ethanol and was stirred for 20 minutes at room temperature. The flask was then placed in an ice bath and then Ethylacetoacetate (2.5 M, 1.63 gm) was added to the same flask and stirring was continued for further one hour. A solution of phosphoryl chloride (0.0065 M, 1.00 gm) in ethanol was added drop wise to the reaction mixture and stirred for one and half hour at the same condition. The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was then filtered and evaporated to dryness by a rotary evaporator. The resultant solid mass was then transferred to a mixture of ethyl acetate and water ethyl acetate: water (1:1). The organic layer was separated, washed with brine and dried over anhydrous Na₂SO₄. The crude product (3.02 gm) was then purified with column chromatography. A yellowish solid product 4A melting point 96⁰C having a yield of 65.36% was obtained. The product was found to be homogenous on TLC plate, R_f value 0.20 (Eathylacetate: n-Hexane = 2:8).

IR (KBr): •_{max}(cm⁻¹) 2921.9 (C-H, CH₃ - C = O), 1633.6 (C = O), 1600.8 (P = O), 1514 (P- Cl), 1450 (P- Cl), 1382.9 (P- C).

GC-MS : m/z 217 (Molecular ion peak).

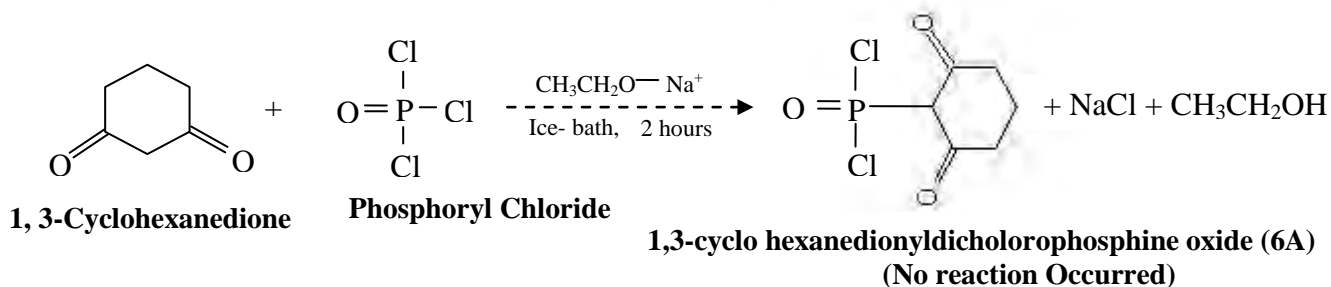
2.5 Synthesis of 1,3- Cyclopentanedionyl dichlorophosphine oxide.

Sodium metal (2.5M, 0.37375 gm) was added to a reaction flask containing 10 ml of absolute Ethanol and was stirred for 20 minutes at room temperature. The flask was then placed in an ice bath and then 1, 3-cyclopentadione (2.5 M, 1.593 gm) was added to the same flask and stirring was continued for further one hour. A solution of phosphoryl chloride (0.0065 M, 1.00 gm) in ethanol was added drop wise to the reaction mixture and stirred for one and half hour at the same condition. The progress of the reaction was monitored by thin layer chromatography (TLC). But no progress of reaction was observed.



2.5 Synthesis of 1,3- Cyclohexanedionyl dichlorophosphine oxide

Sodium metal (2.5M, 0.37375 gm) was added to a reaction flask containing 10 ml of absolute Ethanol and was stirred for 20 minutes at room temperature. The flask was then placed in an ice bath and then ethylcyanoacetate (2.5 M, 1.82 gm) was added to the same flask and stirring was continued for further one hour. A solution of phosphoryl chloride (0.0065 M, 1.00 gm) in ethanol was added drop wise to the reaction mixture and stirred for one and half hour at the same condition. The progress of the reaction was monitored by thin layer chromatography (TLC). But no progress of reaction was observed.



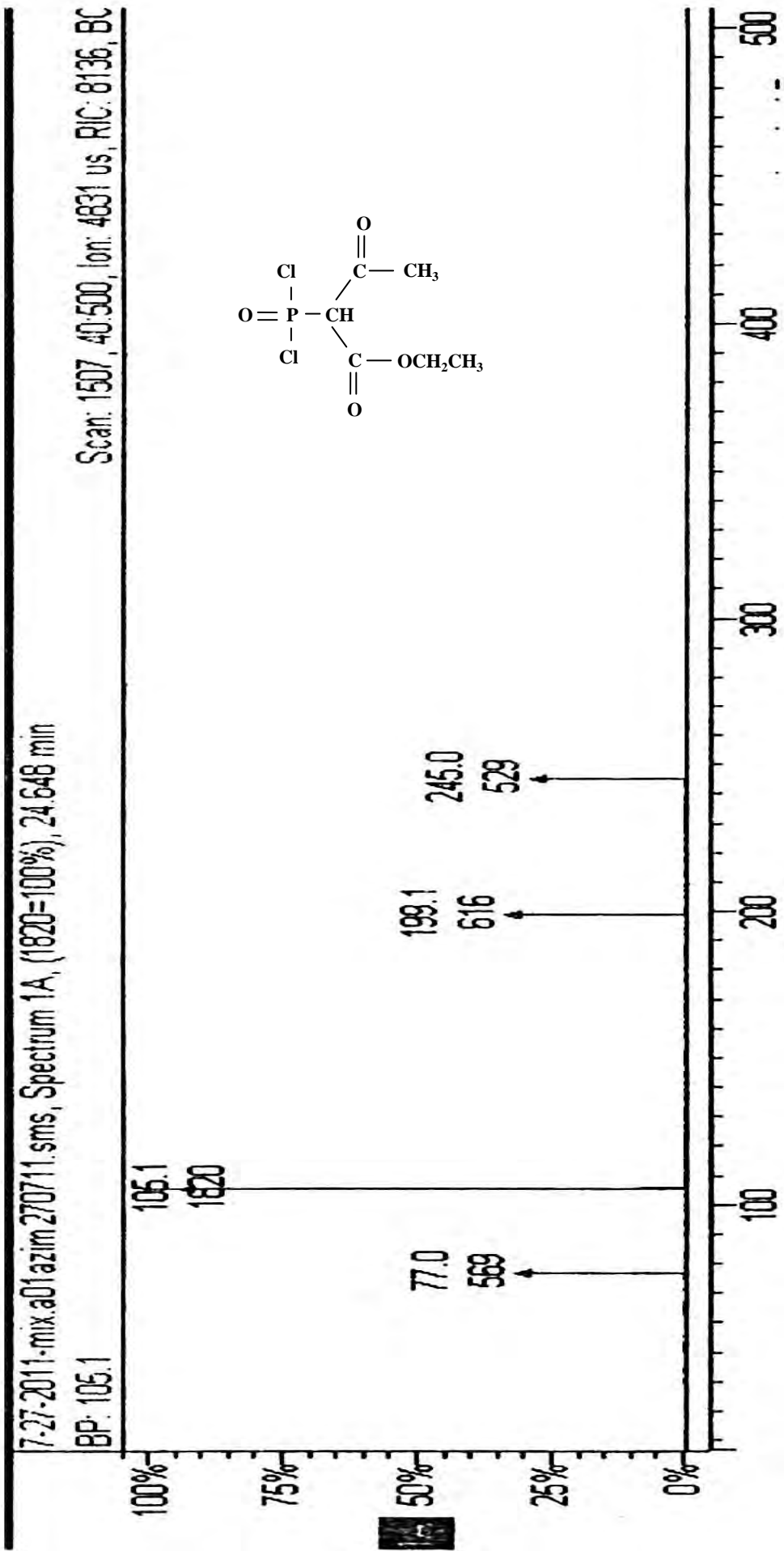


Fig. 1b: GS-MS Spectrum of Compound 1A

7-27-2011-a2 azim 270711.s.ms, Spectrum 1A, (258=100%), 26.172 min
 BP: 55.1
 Scan: 1640, 40:500, Ion: 15722 us, RIC: 4436, BC

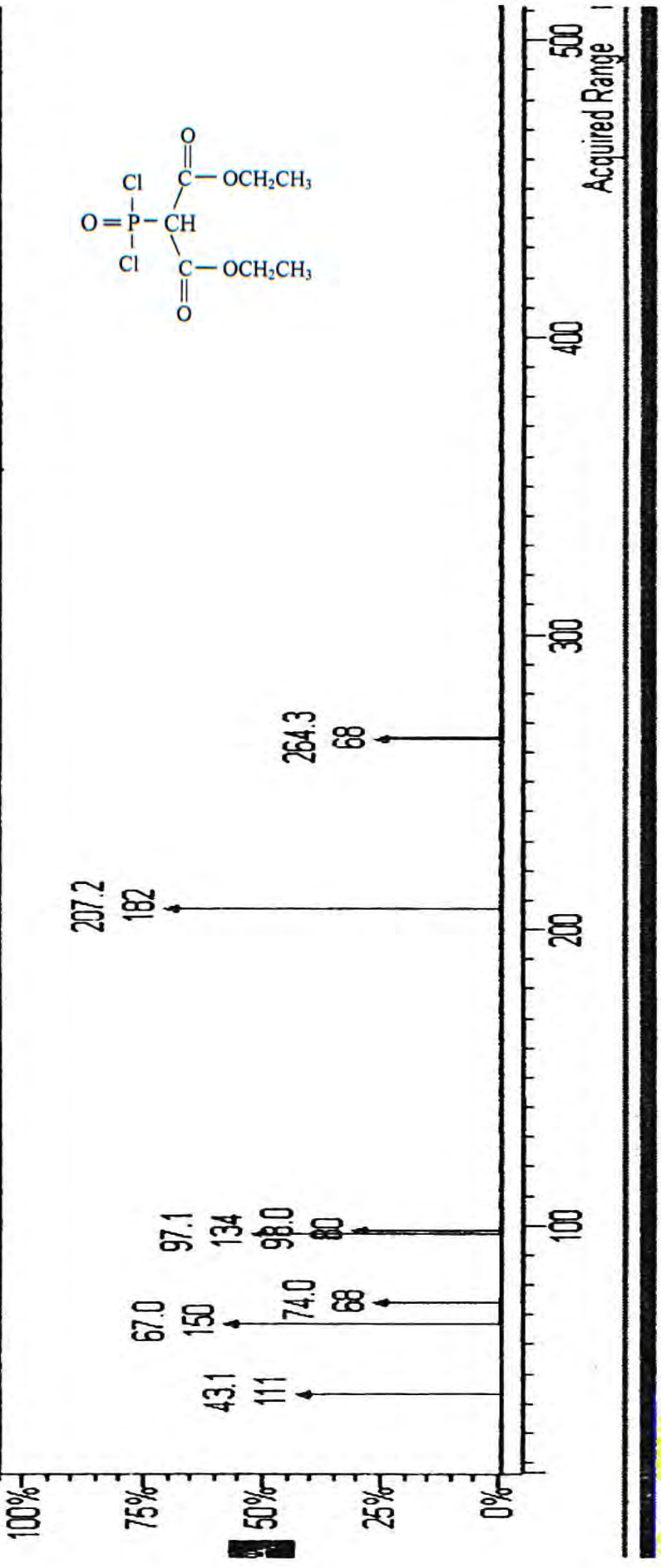


Fig. 2b: GS-MS Spectrum of Compound 2A

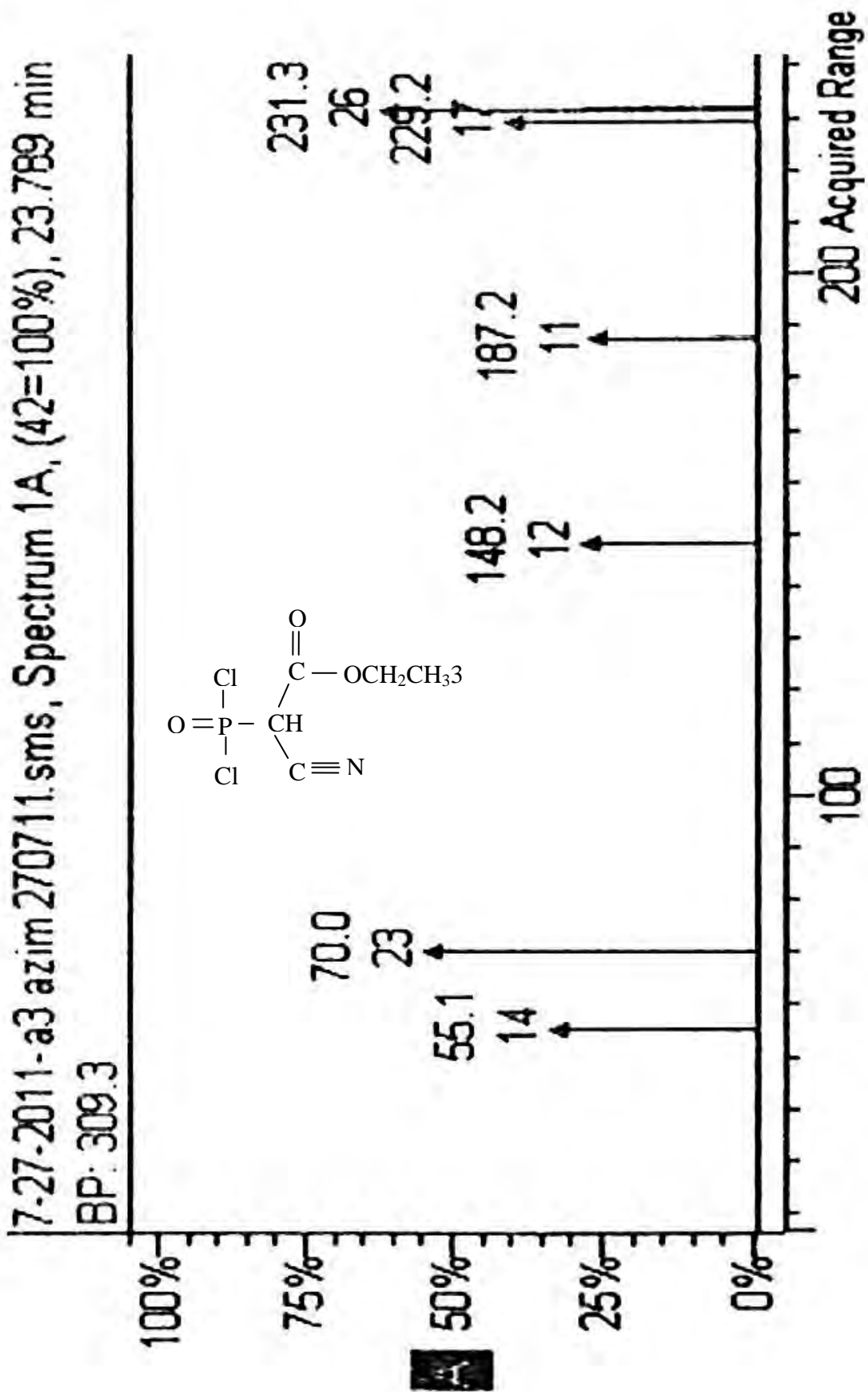


Fig. 3b: GS-MS Spectrum of Compound 3A

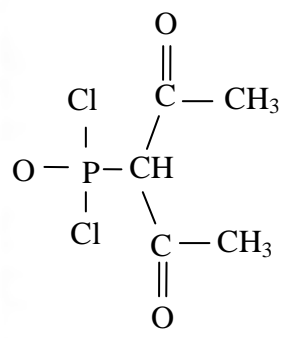
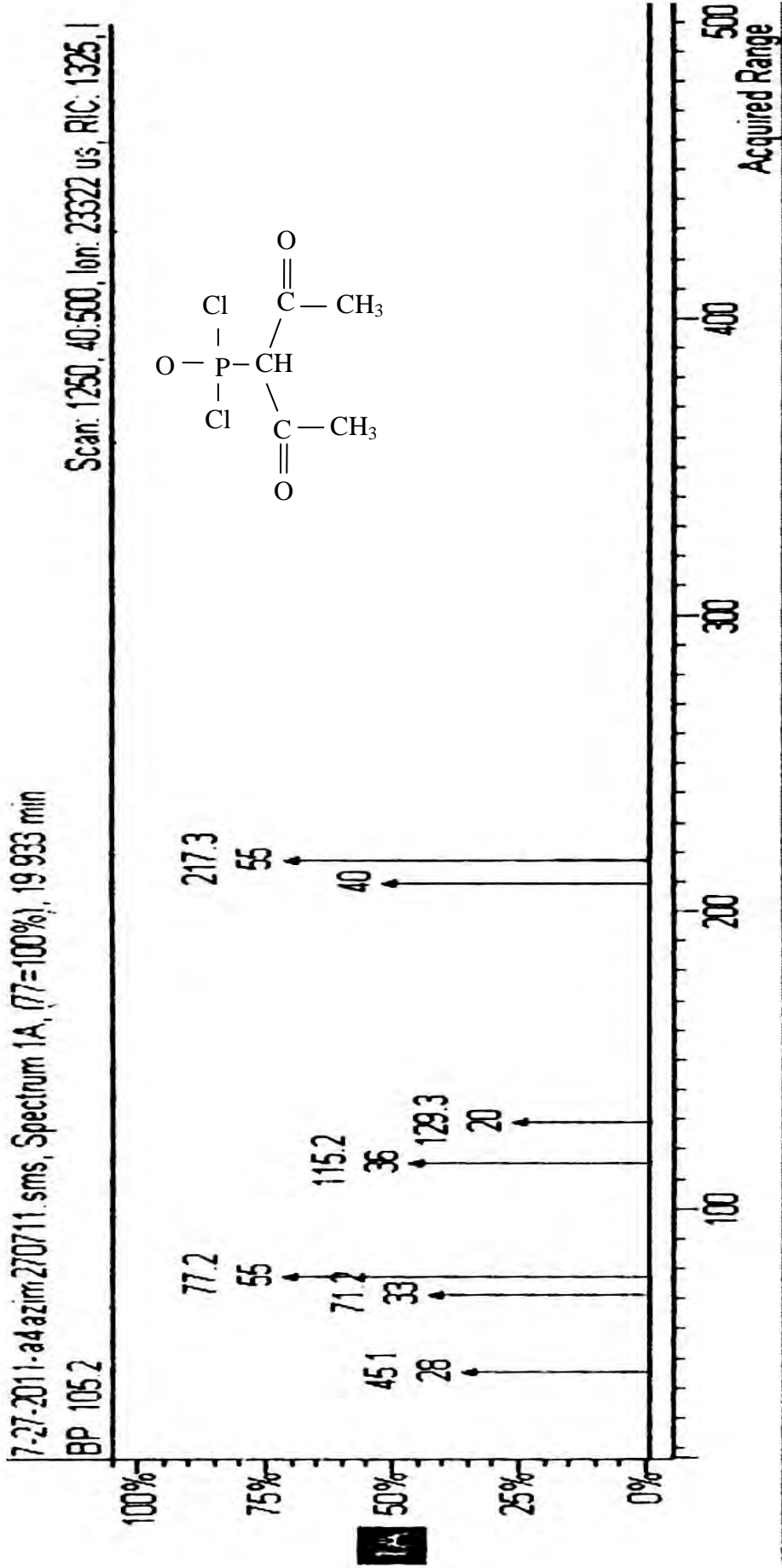


Fig. 4b: GS-MS Spectrum of Compound 4A

Chapter 1



INTRODUCTION

Introduction:

The term “Organophosphorus compounds” are reserved for compounds containing phosphorus and carbon. Compounds containing P• C linkages are usually known as organophosphorus compounds. The most significant organophosphorus compounds are phosphate esters which are based on P• O• C linkages. Phosphorus chemistry is dominated by oxyphosphorus compounds¹⁻², containing phosphorus-oxygen linkages and usually known as phosphates.

Approximately all naturally occurring phosphorus compounds contain phosphorus-oxygen linkages and those of biochemical³⁻⁴ importance are organic phosphate esters containing phosphorus-oxygen-carbon linkages. Organophosphorus compounds which have phosphorous-carbon linkages constitute the second most important group and those containing phosphorous-nitrogen linkages are probably the third. Widespread phosphorous compounds are found on the earth. Phosphoric acid is the most important industrial commodity based on phosphorous. The organic phosphate ester known as deoxyribonucleic acid (DNA)⁵ is present in all life forms and lies at the heart of biochemistry and genetics⁶. It is the most crucial phosphorus compound for the survival and development of the human race concerned. Organophosphorus compounds play a vital role in living process and is essential for the growth, development and maintenance of all plants and animals. These phosphorus compounds are present in soil, bones, teeth, blood and in all cellular organisms. Reversible phosphorylation is the most universal mechanism employed in nature for regulating the action of enzymes and other proteins involved in biochemical processes.

Phosphorus compounds are essential for nitrogen fixation⁷ and the operation of the natural nitrogen cycle which enables the later element to be assimilated by plants. Nitrogen and phosphorus are present in all forms of life where they are essential and they constitute very roughly about 3% and 1% respectively of the total weight.

Although naturally-occurring phosphorus compounds are almost invariably non-toxic but some known synthetic products show a very wide range of toxicity. Most inorganic phosphates based on penta valent phosphorus are among the safest of all substances known to man. They are essential for nutrition and consumed in food and soft drinks and are taken as tonics and

medicines. The varieties are employed in tooth pastes and detergents are completely harmless. No deaths or illness have resulted from these phosphates being present in water, food or other commodities.

Although inorganic phosphorus compounds remain by far the most important commercially, the chemistry of organophosphorus compound has evolved rapidly and now represents a sizeable and explosively expanding part of the whole. There are four major classes of phosphorus compounds:

- i) Oxyphosphorus compounds which contain covalent P• O linkages.
- ii) Organophosphorus (carbophosphorus) compounds which contain P• C linkages.
- iii) Azophosphorus compounds which contain P• N⁸⁻¹⁰ linkages.
- iv) Metallophosphorus compounds which contain P-metal linkages.

It will sometimes be useful to classify phosphorous compound in accordance with the presence of two characteristics bonds e.g.

C - P - O	Organo-oxyphosphorus compound
N - P - O	Azo-oxyphosphorus compound
N - P - C	Azo-organophosphorus compound
M - P - N	Metallo-azaphosphorus compound
M - P - O	Metallo-oxyphosphorus compound
N - P - C	Azo-organophosphorus compound
M - P - C	Metallo-organophosphorus compound

The applications of phosphorous compounds are of diverse nature. The commercial production of orthophosphates and polyphosphates greatly exceeds that of all other compounds of phosphorus. Phosphate esters although produced in smaller quantities have very diverse but important applications. Substituted phosphates particularly phosphonates and thioated derivatives also have a considerable number of current uses. Prominent amongst these are in pesticides, heavy metal extraction, oil additives and polymers of various kinds. Industrially produced natural products such as casein and lecithin have a growing number of applications in food products and other areas.

The utilizations of phosphorus containing organophosphorus compounds are as follows:

- (i) Pesticides
- (ii) Food technology
- (iii) Animal foodstuffs
- (iv) Industrial phosphate esters
- (v) Fertilizers
- (vi) Toxic ester & Medicinal compounds
- (vii) Synthetic polymers and fire retardants
- (viii) Detergents
- (ix) Metal surface treatment
- (x) Glasses
- (xi) Cements, refractories and constructional materials
- (xii) Dental and medical materials
- (xiii) Natural products

1. In Pesticides:

One of the most important applications of organophosphorus compounds is in pesticides as an alternative to chlorinated hydrocarbons which persist in the environment in pesticides^{11-15, 45-48}.

There are mainly two main groups of pesticides: insecticides and herbicides. There are also other crop-protection agents such as fungicides, acaricides, rodenticides, bactericides nematocides, molluscides, fumigants, chemosterilants, insect repellants and other specialized products. It is also convenient to group with these certain crop improvement agrochemicals which are not fertilizers. Some pesticides are very specific in action and may be effective against only one or two species while other may be broad spectrum and effective against wide range of pests.

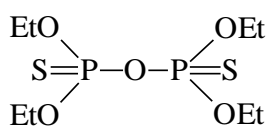
Pesticidal compounds sometimes have more than one function and may act as both insecticides and herbicides or as insecticides and fungicides. Most pesticides are sprayed or dusted as dispersion in an inert carrier. Spraying is almost invariably in the form of an aqueous solution and in the case of dusting the carrier is a finely ground cheap mineral of some kind. Direct

application of pesticide granules to the soil for subsequent root absorption is sometimes used and application to the whole plant in gaseous or smoke form is also occasionally employed. Seed treatment is another technique which has some success.

The ideal insecticide needs to be highly toxic to the insect pest concerned but at the same time be non-toxic to the operator, the plant and the crop consumer. Persistence in action and cheapness are also necessary. A high persistence is desirable if used early in the growing season and low persistence if applied later.

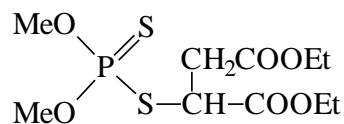
Many insecticides are also classed as acaricides and nematocides. Acaricides deal particularly with mites which attack plants and nematocides deal particularly with leaf, stem and root parasites known as nematodes. Besides, carbamates and organic chlorine compounds other commercially important insecticides belong to organophosphorus compounds.

Some typical organophosphorus insecticides are listed below:



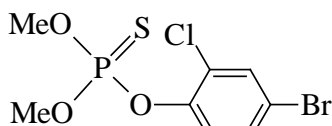
Sulphotep

(1)



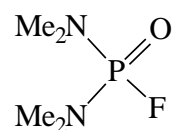
Malathion

(2)



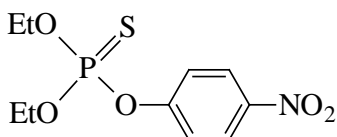
Bromophos

(3)



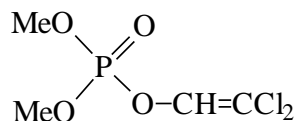
Dimethox

(4)



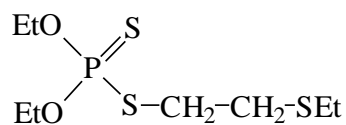
Parathion

(5)



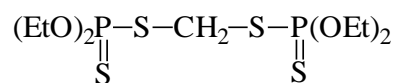
Dichlorvos

(6)



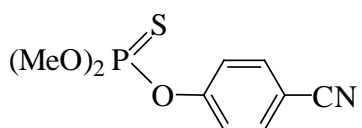
Disul photon

(7)



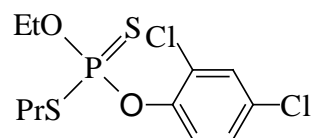
Ethion

(8)



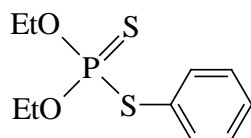
Cyanophos

(9)



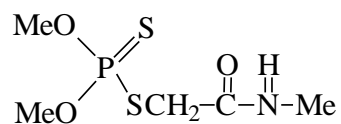
Prothiphos

(10)



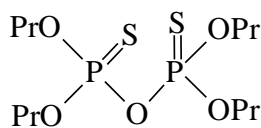
Fonophos

(11)



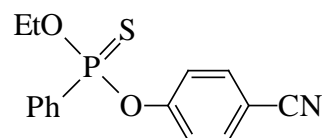
Dimethoate

(12)



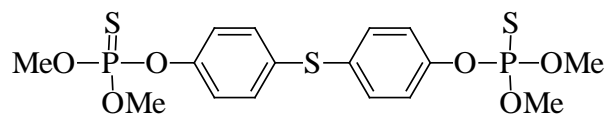
Aspon

(13)



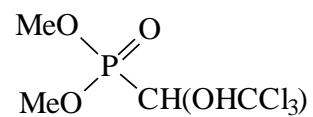
Cyanofenfos

(14)



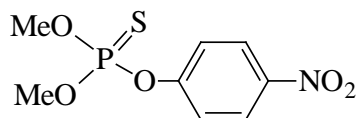
Temephos

(15)



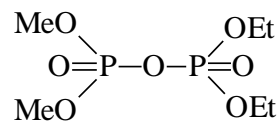
Dipterex

(16)



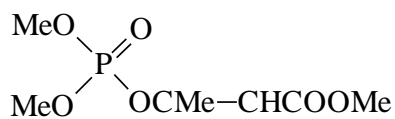
Methyl Parathion

(17)



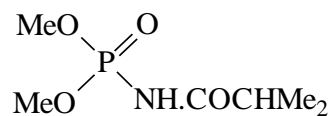
TEPP

(18)



Mevinphos

(19)



Avenin

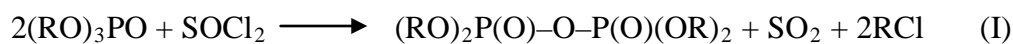
(20)

Several thousand organophosphorus compounds are known to act as insecticides and about 250 of these are manufactured commercially. New compounds are constantly being patented.

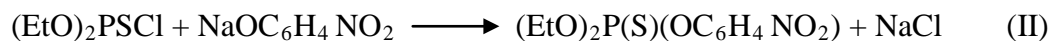
Organophosphorus compounds owe their activity to their capacity to phosphorylate and inhibit the action of cholinesterase although in some instances the inhibition of other vital enzymes is believed to be involved.

Organophosphorus compounds show wide range of properties some being highly specific in action while others are effective against a wide range of pests. Some of the compounds are also extremely toxic to humans. Others are relatively harmless and almost non-toxic to humans. Thio-derivatives are often considerably less toxic to mammals than their oxy analogues although their insecticidal activity is not diminished. Some compounds are non-toxic 'in vitro' but are converted to insect metabolism. Organophosphorus insecticides are generally rapid acting, highly effective in small concentrations and have a low persistence, being easily broken down afterwards to non-toxic materials. Their main drawbacks are relatively high cost and often immediate toxicity should, ideally, become quickly effective after application but subsequently be easily decomposable by moisture thus ensuring that toxic material does not reach the crop consumer. Persistence of organophosphorus insecticides is related to water solubility, vapour pressure and hydrolytic stability, properties which can vary greatly from one insecticide to another.

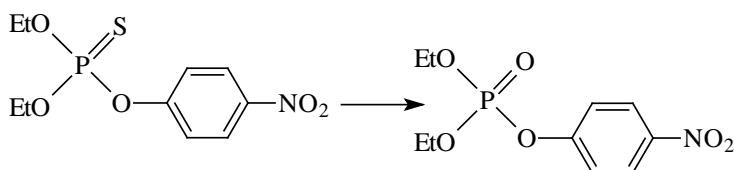
After application and function, organophosphorus insecticides are detoxified and dissipated in the environment by a variety of degradative process. These include hydrolysis, photolysis and bacterial breakdown enzymes being involved in many cases. The first compounds used as insecticides were very toxic to humans and they included TEPP (18), HETP (mainly TEPP), Parathion (5). These compounds while effective against a wide range of pests could easily be absorbed through the skin and were very dangerous to use. Several fatalities occurred when they were first employed on crops. Like most nerve gases however the toxicity of organophosphorus insecticides is usually removed on hydrolysis. In fact the removal of insecticide residuals by rain water is often relied upon before crop harvesting. One technical process used to prepare TEPP was the chlorination of trialkyl phosphates with thionyl chloride (I) but the product is now almost obsolete because of its hydrolytic instability as well as toxicity.



The highly toxic parathion (5) discovered in 1944 by Schrader has a water solubility of 24 ppm and can be made by reaction (II). It has a greater hydrolytic stability than TEPP and is consequently more persistent in action.



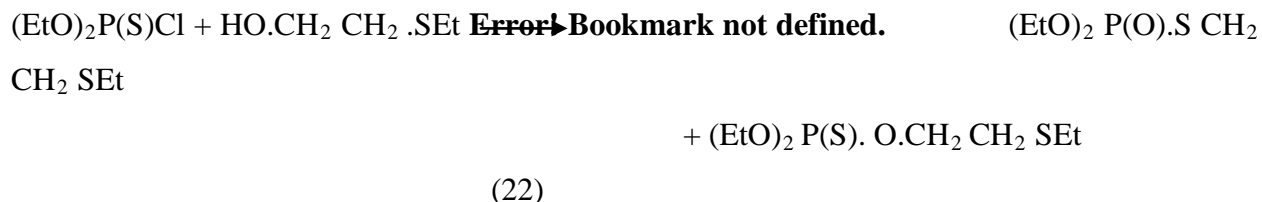
Conversion to a phosphoryl derivative is necessary for insecticidal action in order that phosphorylating action can ensure and the compound becomes active. In the case of parathion this may happen by thiono to thiolo isomerisation (21).



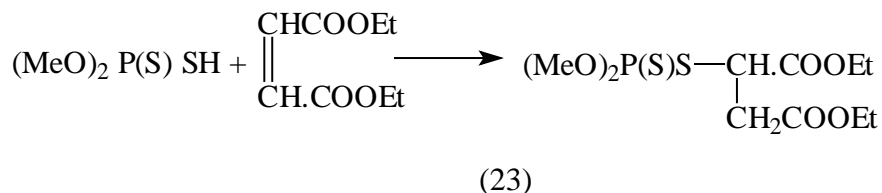
(21)

Parathion itself is less toxic but without phosphorylation it can't be active as insecticidal action. Dimeton (Systox) is a mixture of thiono and thiolo isomers.

It can be made by reaction (22). The thiolo isomer has 10 times the toxicity and 100 times the solubility of the thiono isomer.



Malathion is made by reaction (23). Like parathion, it is only slightly water-soluble, but it is more easily hydrolysed than the latter.



2. In food technology

Phosphates¹⁶⁻²² are present in most natural foods, particularly in meat, milk and dairy products, fruits and in cereals. Further addition of phosphates is frequently made in the processing of foods for a variety of purposes which include for increasing nutritive value for complexing of undesirable metal ions, preservation, prevention of caking, leavening action, color development or stabilization.

The major phosphorus-containing products in current use as food additives may be listed as:

- (i) Inorganic salts – polyphosphates, mostly of sodium, potassium or calcium.
- (ii) Biopolymer²³ phosphates – casein, lactalbumins phosphates, starch phosphates, lecithin.

Medicinal supplementation of phosphorus is usually with casein, orthophosphates of glycerophosphates of sodium, potassium or calcium. The applications of phosphorus

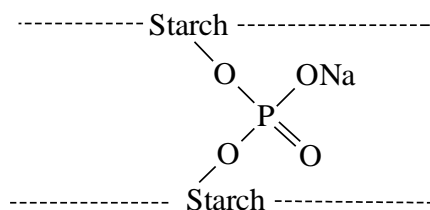
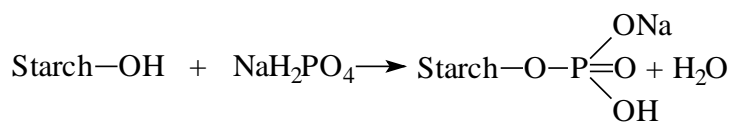
compounds are exceedingly numerous in the field of food technology such as in milk and dairy products, meat and fish, fruit and vegetables, beverages, leavening agents, biopolymer phosphates etc.

The chief mineral constituents of milk are phosphorus and calcium together with sodium, potassium, magnesium and minor quantities are citric acid and a great deal of water. The phosphorus content (about 0.95 g of P/liter in cow's milk) is distributed between more than 50 different compounds both organic and inorganic. Most abundant and important of these are the casein phosphoproteins, calcium phosphates and the phospholipids. Other phosphorous compounds present in much smaller quantities are most of the vitamins, various nucleic acids, enzymes, sugar phosphates and protease, peptones (phosphoglycopeptides).

About 2.0% of H_2PO_4^- anions are present in natural citrous fruit juices as well as about 0.02% glucose-6-phosphate and other sugar phosphates. Other phosphorus compounds present in relatively minor quantities are nucleic acids, adenosine tri phosphate (ATP), phospholipids and B group vitamins. Very useful effects are observed by treatment of fruit and vegetables with added phosphates. These include stabilization against bacteria and rancidity enhancement of color and desirable effects on tenderness and firmness. For example, small additions of tetra sodium phosphate ($\text{Na}_4\text{P}_2\text{O}_7$) to peas and beans prior to canning lead to a tenderer product due to the sequestering of calcium ions.

The addition of sodium polyphosphates stabilizes the color of strawberries, tomatoes, cherries etc. and the use of such compounds prior to canning or freezing will help to keep vegetables green²⁴. Pyrophosphates such as di-sodium hydrogen phosphate (Na_2HPO_4) are used to counteract the blackening of raw potato or apple juice which is due to the oxidation of diphenolic compounds in the presence of heavy metal ions. The later are removed by complexing with the pyrophosphate ions.

Starch phosphates²⁵⁻²⁶ are being increasingly used in manufacturing since they promote thickening without jelly form. Starch phosphates have a fairly low degree of $-\text{OPO}_3$ substitution for $-\text{OH}$ and are obtained by heating starch with phosphoric acid at about 60°C . Some natural potato starch already contains a few phosphate ester groups.



Sodium dihydrogen phosphate reacts with starch to give a monoester salt while sodium trimetaphosphate reacts to produce cross linked diester. Cross-linked varieties of these kinds are more stable towards heat, agitation and acidity than monoester salts.

Corn starch processed with cyclic sodium trimetaphosphate is used to make cold-water jellies. Phosphorylated varieties of this kind are resistant to hydrolysis and degradation probably due to cross-linking and are used as thickening agents in cooked foods. Starch phosphates are useful in frozen foods where they impart good freeze-thaw stability and reduce retro gradation. The stability of ice cream and other products can be improved. Starch phosphates can be used as cheese emulsifiers and phosphates incorporated into flour will improve its properties by reaction with the starch. Phosphates can be employed with advantage to improve the properties of starch gelling materials as gelatin, pectin, and alginate as well as starch.

Sugar phosphates used in foods are relatively few in number they include the improvement of the crispness of breakfast cereals²⁶ and the flavour of alcoholic beverages²⁶.

Casein is used as a nutrient²⁷⁻³¹ additive to fortify flour, bread, biscuits and breakfast cereals and is often used as a component of coffee whiteners. It emulsifies, imparts body and improves flavour of the later. Sodium caseinate is used as a binding agent in saucages and related products and as an extender in meats and soups where it imparts smoothness, creaminess and consistency as well as emulsifying and adding to nutritive value. Casein is used to improve the desired properties of such diverse products as the protein chocolate, synthetic caviar, imitation cheese, macaroni, yoghurt, effervescent lemonade powders, ice cream, instant pudding and desserts and simulated meat.

Edible casein fibers can be obtained by spinning an aqueous solution or slurry of a casein salt, into coagulating bath or directly into air. Yet another use for casein is for stabilization, color removal and clarification of beer and white wine. Casein is listed as a component of various dietary and infant foods.

Phospholipid such as lecithin which is available in various grades is widely used in the food industry as a surfactant, an emulsifier and an anti-oxidant. Lecithin is used in baking where it acts as an emulsifier, a wetting agent to reduce mixing time, a parting agent to affect cleaner and easier release from moulds and an anti-oxidant to stabilize vegetable and animal fats. Dough-handling properties are improved with lecithin and other improvements are secured in biscuits, pies, cakes and waffles. Lecithin improves the cheese yield from milk³¹ It is also introduced into foods in the form of egg yolk where it may act as an emulsifier as in mayonnaise and salad dressings. The emulsifying properties may be due to the formation of a lecithin-protein complex. The function of egg yolk lecithin in foods is complicated and is not necessarily quite the same as that of commercial ex-soy bean products.

Synthetic organophosphorus compounds are used in food processing and the use of poly-substituted tri-arylphosphine compounds as anti-oxidants and poly (*p*-diphenyl phosphino) styrene retards the formation of peroxides in sunflower oil.

Hydrophosphorous acid or its salts can be used to block the formation of carcinogenic nitrosamines (from nitrites) in smoked fish

3. In Animal foodstuffs

The phosphorus contents of most animal foodstuffs are not particularly high and the more restricted variety of their diet makes animals much more prone to phosphorus deficiency than humans.³⁰⁻³³ Phosphorus deficiency is the most wide spread and economically important of all mineral deficiencies affecting grazing livestock.

Phosphorous is absorbed as soluble phosphate in the duodenum. The amount of absorption of phosphorus from the dietary input is influenced by many factors. These include the type of food,

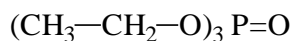
animal age, internal pH and the intake of other elements such as sodium, potassium, calcium, iron, aluminum, magnesium and zinc. Excessive iron, aluminum, magnesium in the animal diet is known to reduce the absorption of phosphorus by forming insoluble phosphates. Mono and di-calcium phosphates are added to animal foodstuff to guard against dietary deficiency of phosphorus. Stock feed di-calcium phosphate, hydrate calcium hydrogen phosphate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) can be made from calcium hydroxide and most wet-process phosphoric acid. Apart from possible reduction of phosphorus absorption, the iron, aluminum and magnesium salt impurities do not seem to be harmful to animals.

Di-sodium hydrogen phosphate (Na_2HPO_4), ammonium phosphate or urea phosphate $\text{CO}(\text{NH}_2)_2 \cdot \text{H}_3\text{PO}_4$ may also be used as supplements to animal feeding³⁴⁻³⁶ compositions. Pyrophosphates and potassium orthophosphates are sometimes incorporated into pet foods. Ammonium phosphates are used in cattle foods.

Lecithin and dehydrated casein are also used as animal food supplements. A useful animal food supplement can be obtained by adding phosphoric acid to molasses. The acid reduces the viscosity of the later as well as increasing its nutrient value. Essential nutrient elements such as copper, iron, and magnesium can be successfully incorporated into slowly soluble glass pellets and fed to ruminant animals. The glass pellet stays lodged in the rumen for several months where it supplies the nutrient element.³⁹

4. In Industrial phosphate esters

Though phosphorous compounds have enormous importance in biochemistry, phosphates esters³⁷⁻⁴³ may have many technological applications. Some of the more important industrial products are listed below:



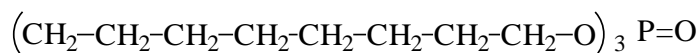
Triethyl phosphate

(24)



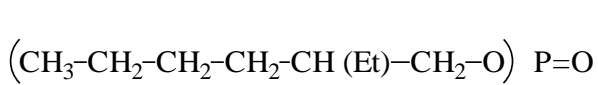
Tri isopropyl phosphate

(25)



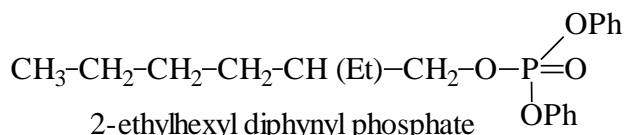
Tri octyl phosphate

(26)



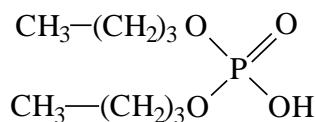
Tris (2-ethylhexyl) phosphate

(27)



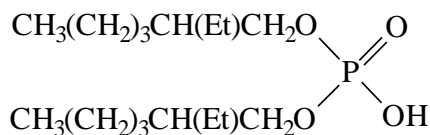
2-ethylhexyl diphenyl phosphate

(28)



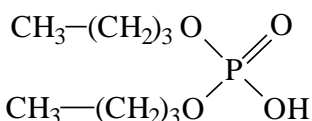
Di butyl hydrogen phosphate

(29)



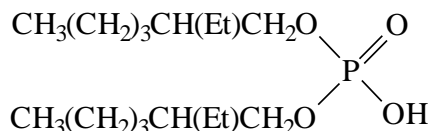
bis (2-ethylhexyl) hydrogen phosphate

(31)



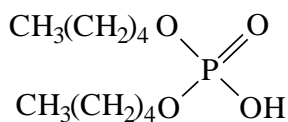
Di butyl hydrogen phosphate

(33)



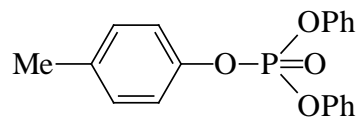
bis (2-ethylhexyl) hydrogen phosphate

(34)



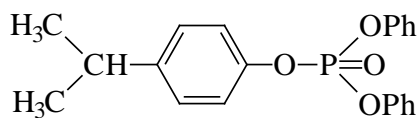
Di pentyl hydrogen phosphate

(32)



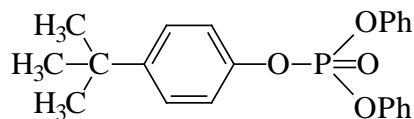
Cresyldi phenyl phosphate

(33)



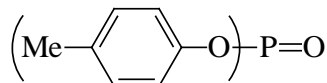
Isopropyl di phenyl phosphate

(35)



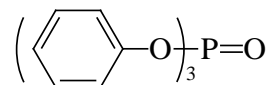
t-butyl phenyl phosphate

(36)



Tri-cresylphenyl phosphate

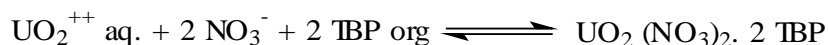
(37)



Tri-phenyl phosphate

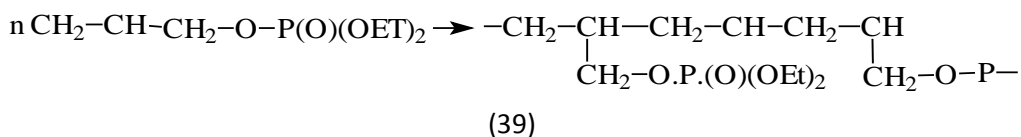
(38)

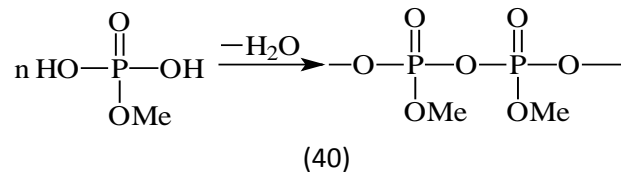
Trialkyl phosphates and lower dialkyl phosphates are liquid at room temperature and show a regular progression in their physical properties. Most aromatic di and tri -esters are solid at room temperature. Triethyl phosphate is miscible with water and like tripropyl and tributyl phosphates, it finds use as a solvents. The use of esters such as tributyl, tricresyl or cresyl diphenyl phosphate results in smoother combustion and improve performance when incorporated as petroleum additives. One function of the esters is to combine with lead from tetraethyl and expel it as relatively harmless lead orthophosphate. Esters confer valuable anti-wear and corrosion inhibition properties when use as oil additives. Tributyl phosphate and related esters such as dibutylphosphate $(\text{Bu}^n\text{O})_2\text{P}(\text{O})\text{OH}$ (DBP) and bis-2-ethylhexyl phosphate (HDEP) have important uses in the extraction of rare earth, actinide and other heavy metals from mineral resources and their recovery from waste products of the atomic energy industry. A solution of trybutyl phosphate (TBP) in kerosene can be used for solvent extraction of uranium and thorium and other rare earths from their mixtures in 10 % aqueous solution in nitric acid. The metal complexes such as $\text{UO}_2(\text{NO}_3)_2[(\text{BuO})_3\text{PO}]_2$ which are formed on mixing the aqueous and kerosene phases can be successively removed from the latter in which they are soluble as



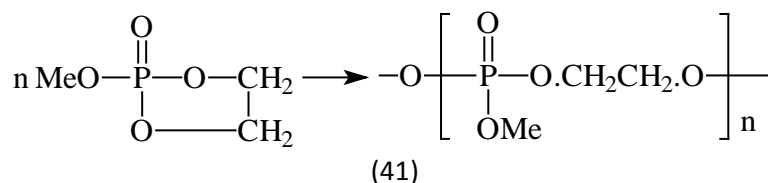
Difference of the extraction coefficients with different cations may be utilized in the separation of uranium, transition metals and rare earths. This is a well established method for the extraction of uranium in the processing of nuclear fuels. Hafnium can also be separated from zirconium by this technique using TBP.

Tributyl phosphate (TBP) is still widely used for the purification of uranium for nuclear reactors and in the re-processing of spent nuclear fuels. Certain phosphate esters can be polymerized to give polymers on their own account (homopolymers) with the phosphorus atom either in the side chain (39) or in the main chain (40). Natural polymers of the later type include the nucleic acids and the techoic acids.



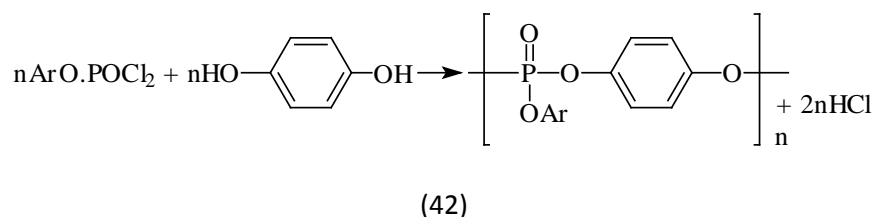


Some 5- and 6-membered ring phosphate esters can be polymerized as methyl ethylene phosphate (41)

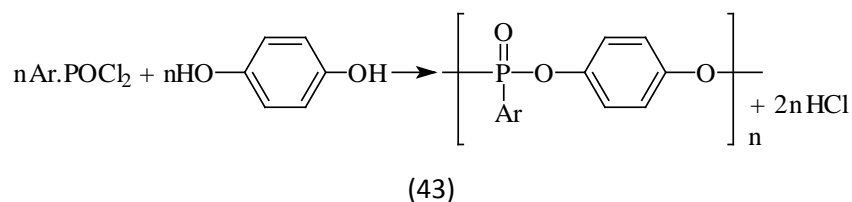


Tris allyl phosphate $(\text{CH}_2 = \text{CH}-\text{CH}_2\text{O})_3\text{PO}$ will give rise to a clear hard cross-linked polymer. Polymerized allyl or vinyl phosphates have not generally led to successful commercial products.

High molecular weight polymers or relatively short chain oligomers can be prepared by the reaction of POCl_3 or aromatic derivatives ArPOCl_2 with some dihydric phenols (42).

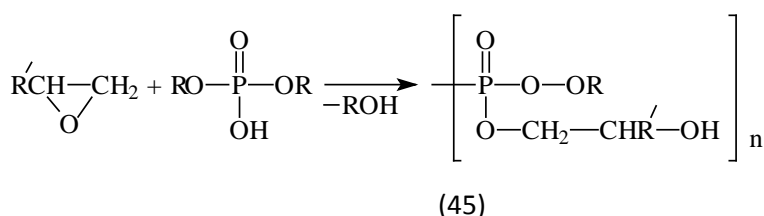
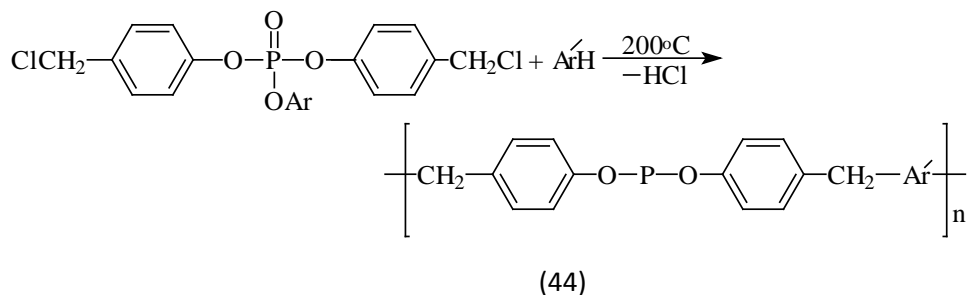


Products of type (42), first obtained about 40 years ago as ‘phoryl resins’ have good flame resistance, high transparency and hardness but they lack resistance to hydrolysis because of the P-O-C linkages are present. Similar polymers based on phosphonates (43)



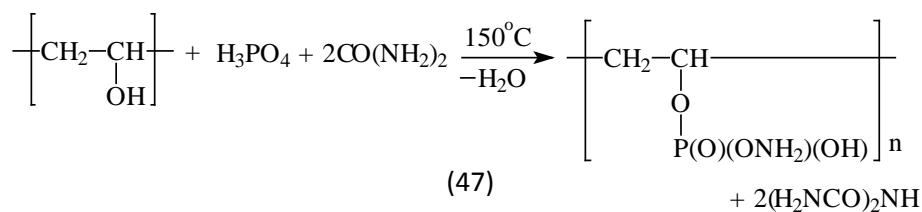
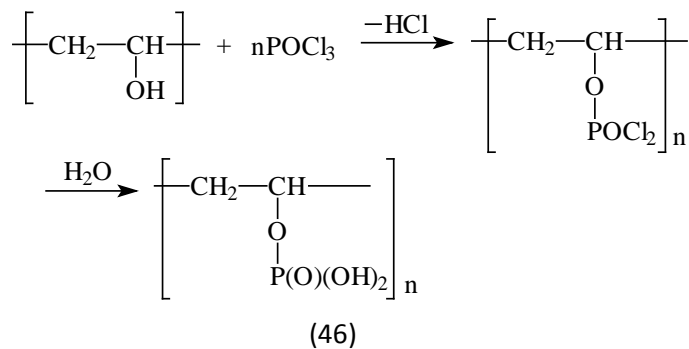
are somewhat more stable but satisfactory stability towards hydrolysis is achieved with chains based on P-C linkages.

The Friedel-Crafts reaction can be used to prepare some polymeric phosphate esters (44) while others can be prepared by co-polymerization of dialkyl hydrogen phosphates with epoxides (45)



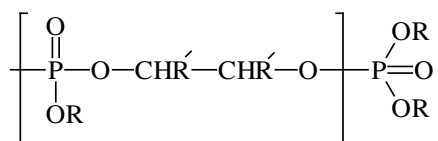
Polyvinyl alcohol can be wholly or partially converted to polyvinyl phosphate by the action of POCl_3 followed by hydrolysis (46). Heating of the polyacid product leads to a cross linked polymer which resists hydrolysis by dilute acids and bases.

The mono ammonium salt is obtained by the action of phosphoric acid and urea on polyvinyl alcohol (47).

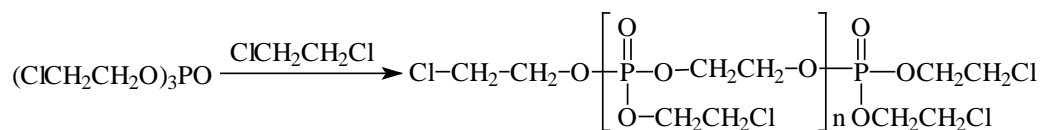


In current practice, polymeric phosphate esters are used almost exclusively as additives to modify the properties of established organic non-phosphorus polymers. This may be achieved either by co-polymerization, chemical bonding to the preformed organic polymer or in some cases merely by physical incorporation.

Various oligomers of the type (48a) have been patented as flame retardant additives for polyurethane foams. One such material can be obtained from tris (2-chloroethyl) phosphate⁴⁴ (48b).



48(a) If R, R' = Short chain alkyl



48(b)

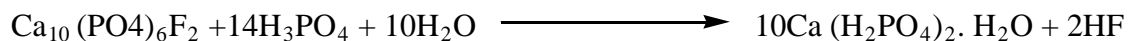
Highly polymerized mono and diesters have been patented as rust preventing polymers.

5. In Fertilizers

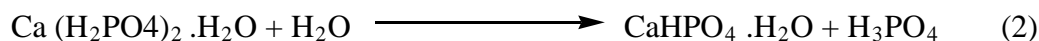
Agrochemicals⁴³⁻⁴⁸ have over the last 50 years exerted an enormous influence on world economic and sociological development. They have generally been a great success in feeding the world's expanding population. Agrochemical can be divided into two major groups as (a) Fertilizers and (b) Pesticides.

Phosphorus containing fertilizer materials were in use for many centuries before their action was identified with the presence of the element. Fish and animal manures were employed several thousand years ago and the Carthaginians were using bird dung in 200 BC. In the twelfth century, guano was used by the Arabs and the Incas. English farms used bones in the seventeenth century and waste bone and ivory chipping from button and knife manufacture in Sheffield were used locally around 1750.

Superphosphate is still an important fertilizer. It is made by the direct action of sulphuric acid on phosphate rock and the active constituent is monocalcium phosphate $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$. A higher grade of fertilizer known as 'triple superphosphate' made by the action of wet process phosphoric acid on phosphate rock. The reaction may be summarized by equation as;



The product contains a higher proportion of available phosphate than ordinary superphosphate and its manufacture has become more economic than the latter, over the last two decades. Reaction such as do not go to completion immediately and reaction periods up to 30 days may be required under some condition. After application to the soil, monocalcium phosphate in the fertilizer is hydrolysed to dicalcium phosphate according to equation as;



Ammonium phosphate fertilizers have assumed a greatly increased importance in recent years and have now become the leading commercial product. Mixtures of the mono and di-salt are obtained from direct reaction of ammonia with wet process phosphoric acid. The tri-ammonium salt is not favoured in fertilizers because of the ammonia on storage.

The popularity of ammonium phosphate fertilizers arises from their high nutrient content of both phosphorus and nitrogen high solubility and good storage and handling characteristics. They are easy to produce and complete economically with the longer established calcium salts commercial products are available as solution, solids or suspensions.

A large part of the organic phosphorus content of soils is provided by bacteria and their dead residues. The major pathway by which phosphorus enters into organic combination in plants through formation of adenosine tri-phosphate (ATP). The latter is generated during photosynthesis and is required by numerous metabolic processes. Among these are the assimilation of nitrogen and sulphur by the plant, the transport of various nutritional ions through cell membranes and the production of plant starch and cellulose.

The phosphorus absorbed by plant cell becomes involved in metabolic processes within a few

minutes and the esters produced include phosphorylation sugars such as fructose-6-phospholipids such as lecithin, nucleic acids and phytic acid salts hexaphosphates. Some microorganisms will convert the organic phosphorus compounds into inorganic phosphates. On the other hand, some varieties of microorganisms. Present on surfaces are able to bring insoluble phosphates into solution, microorganisms also 'immobilize' available phosphates in soil solution by converting them into cellular material.

6. Toxic ester & Medicinal Compounds

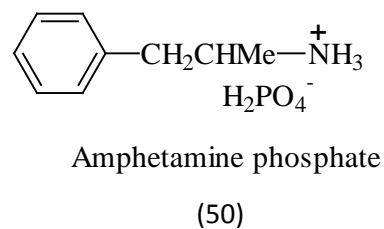
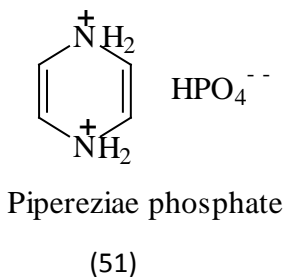
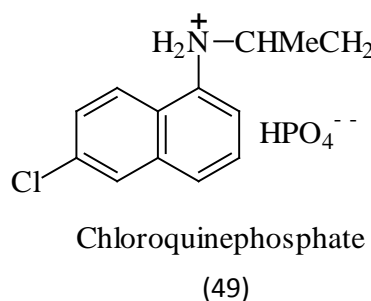
Organophosphorus compounds have some uses in medicinal compounds. Some inorganic phosphorus compounds⁴⁹⁻⁵⁶ such as inorganic phosphate salts have long been established medicinal uses. These include stomach antacids such as hydrated magnesium phosphate and aqueous suspensions of composition $\text{AlPO}_4 \cdot \text{XH}_2\text{O}$ (Phosphagel). Mixtures of di-sodium hydrogen phosphate or di-potassium hydrogen phosphate ($\text{Na}_2\text{HPO}_4/\text{K}_2\text{HPO}_4$) can be used for the treatment of phosphatemia (Phosphorus deficiency).

The wide variety nature of diets in western countries prevents the occurrence of phosphatemia which is quite rare in humans, an excess of phosphorus⁵⁷⁻⁵⁸ in the diet however, may lead to a reduced absorption of other essential trace elements and hence a deficiency of them may be observed. Phosphate salts make the urine more acidic and prevent the deposition of calcium salts as urinary stones. Dicalcium phosphate dihydrate ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) with the correct particle size distribution is particularly useful as a diluents and stabilizer in the preparation of pharmaceutical tablets by dry compression.

It is insoluble, compressible, non-toxic, stable in storage and usually inert to the other ingredients, moreover it assists in the flow and bonding of the latter. Various calcium phosphates are used in artificial bone formulations in dental practice and in toothpaste formulations. Hypophosphite salt have found applications tonics and as anti-oxidants in pharmaceutical preparations. Amorphous zirconium phosphate $\bullet\text{-Zr}(\text{HPO}_4)_2$ is an excellent sorbant for use in renal dialysis.

Radioactive chromium phosphate ($\text{Cr}^{32}\text{PO}_4$) is a neoplastic suppressant and is much used in cancer treatment. The heteropoly anion $\text{P}_2\text{W}_{18}\text{O}_{62}^{6-}$ is a potent inhibitor of viral di-oxy nucleic acid (DNA) but other more complex anions of this type may prove to be more useful. Radioactive ^{31}P has various uses in medicine. Another area, potentially of great importance is the use of slightly soluble phosphate glasses as carriers of pharmaceutical⁵⁹ compounds. Implants of such materials can act over long periods for slow release into the bloodstream or infected organs⁶⁰⁻⁶¹. Tooth implants of phosphate glass impregnated with anti-carries compounds may prove to be effective against tooth decay.

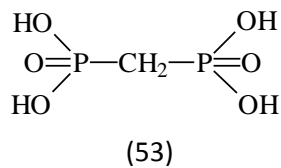
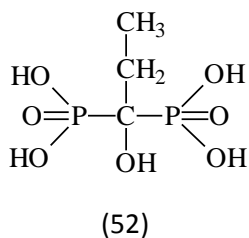
A number of well known phosphate salts of organic drugs⁶²⁻⁶⁴ are prescribed as medicines. This is because the phosphate generally causes fewer disturbances to physiological pH, it may have a more suitable solubility or merely because it is the salt most conveniently prepared and purified. Examples are;



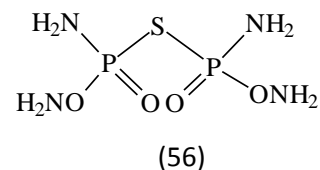
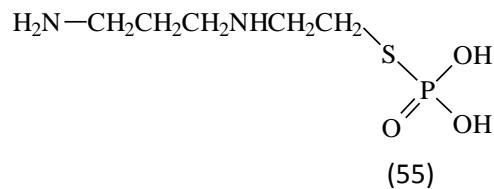
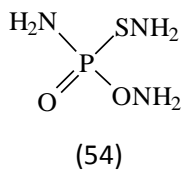
Chloroquinephosphate is used as anti-malarial drug, amphetamine phosphate is used as anti-depressant and piperazine phosphate is used as anthelmintic drug.

Ethane-1-hydroxy-1, 1- diphosphonate (EHDP) (52) and related compounds such as (53) inhibit bone resumption and are used in the treatment of bone disease. Complexes of the diphosphonic acid with x-ray emitting isotopes of technetium are useful for medical diagnostic work since they concentrate in the bone. The use of technetium diphosphonate complexes for bone imaging (MRI) has revolutionized bone scanning techniques. Technetium pyrophosphate complexes are less satisfactory since the P-O-P linkages are liable to hydrolysis by body enzymes.

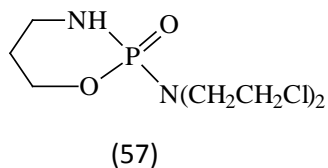
Iron complexes of phosphorylated mono and disaccharides will function as contrast agents in the MRI of the gastrointestinal tract.



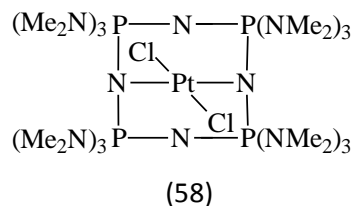
A number of phosphorothioates show anti-radiation activity and are excellent radioprotective agents. Some of these compounds are listed below.



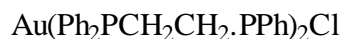
In the recent years an important advance was made in the discovery of the carcinostatic properties of cyclophosphamide (57) and its derivatives.



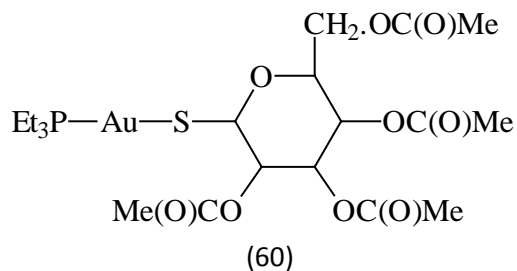
The platinum complex (58) has similar properties.



Phosphine-gold complexes such as (59) have recently been found to be very effectively in the treatment of rheumatoid arthritis. Auranofin (60), unlike other anti-arthritic gold compounds, can be administered orally.

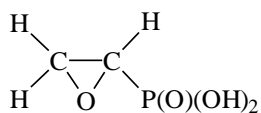


(59)

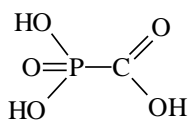


(60)

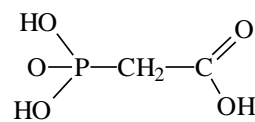
Phosphonomycin (61), Phosphonoformic acid (PFA) (63) and phosphonoacetic acid (PAA) (63) are among the earlier compounds found to have anti-viral properties. Phosphonoacetic acid is active against Herpes Virus and Marek's disease while phosphonomycin shows anti-bilharziosic and anti leprosy properties as well as functioning as a broad spectrum antibiotic⁶²⁻⁶⁴.



(61)

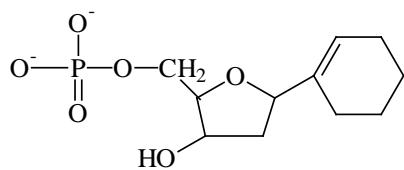


(62)

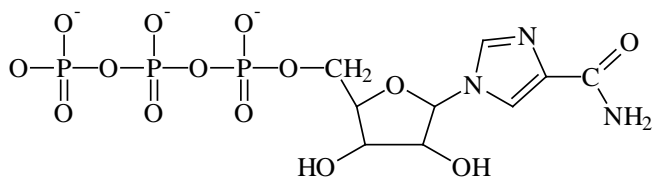


(63)

Much studied ribavirin (64) known since 1972 and 5-Fluoro-2-deoxyuridine -5- phosphate (65) is an anti-cancer drug⁷⁵⁻⁷⁷.

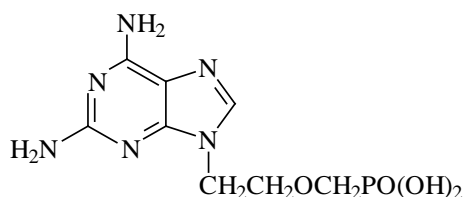


(64)

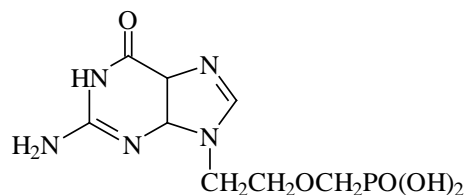


(65)

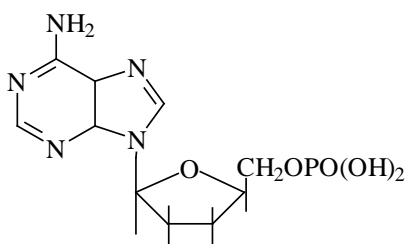
The three phosphonates (66-69) show strong activity against HSV or HIV and (67) is typical of the 2', 3' di-deoxynucleotide derivatives which have antiviral activity.



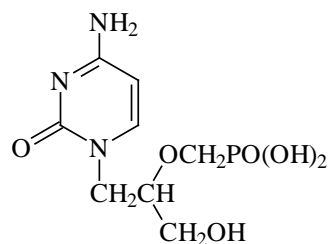
(66)



(67)

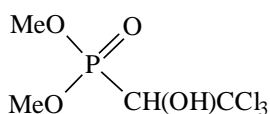


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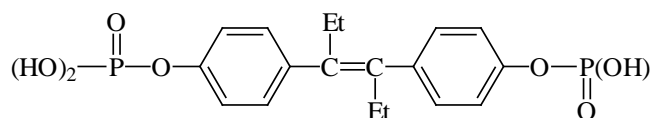


(69)

Metrifonate (70) is used for the treatment of urinary tract infections and diethylstilbestrol bisphosphate (71) can be used in the treatment of prostatic carcinoma.



(70)



(71)

7. In synthetic polymers and fire retardants

Application of phosphorous containing synthetic material or synthetic polymer⁶⁵⁻⁶⁷ has many considerable advantages. Numerous polymerized products containing phosphorus are based on P- C linkages and are generally more difficult to prepare than those based on P -N- C linkages.

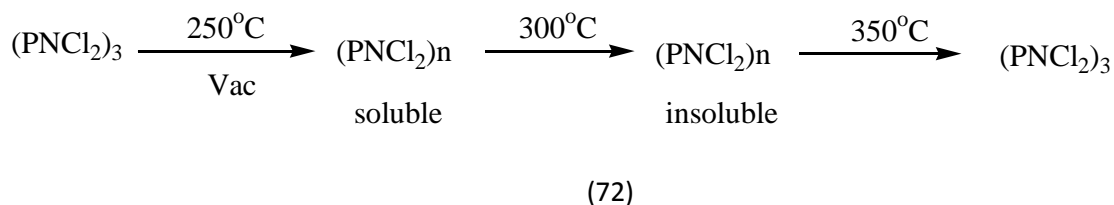
Some phosphorus containing monomers can be self condensed to form homo-polymers while others can be co-polymerized with a non-phosphorous containing monomer. Desirable commercial properties are sought in polymers of the latter type which employ a minimal amount of the usually more expensive phosphorous compound.

The major application of organophosphorous polymer has so far been in flame proofing and fire-retardancy but they have also found an important role in the modification of the properties of established non-phosphorous polymers. In addition, growing applications lie in the areas of ion-exchange materials, surface additives, catalysts and tooth preservation agents.

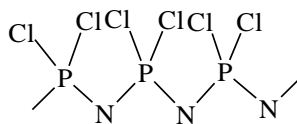
Some phosphorus containing compounds are highly polymeric product. One such highly polymeric product is phosphonitrilic rubber⁶⁶⁻⁶⁸. This can be made directly by heating cyclic trimer in the region of 250-300°C the polymer prepared in this way is a soft colorless transparent soluble elastomer consisting of simple linear chains with a rather broad molecular weight distribution.

On stretching phosphonitrilic rubber a considerable degree of chain alignment takes place and the rubber changes from amorphous to crystalline, X-ray analysis of such drawn fibers has shown the polymer consists of continuous chains spiraling along the drawn fiber axis.

This polymer is soluble in benzene or toluene to form a highly viscose solution. Molecular weight measurements indicate this type of material has a chain length of 200 or more PNCl_2 units.



If polymerization is carried out for longer periods at the upper end of the temperature range, a moderate degree of cross-linking of the chains is induced. This cross-linked material is tougher and more rubbery and it swells when in contact with organic solvents rather than dissolving in them.



(73)

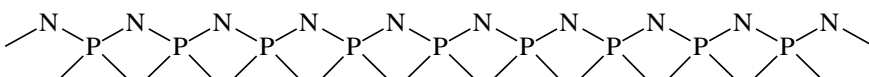
Both polydibromophosphazene $(\text{PNBr}_2)_n$ and polydifluorophosphazene $(\text{PNF}_2)_n$ are pale amber or colorless rubbery solids which can be prepared by heating their respective cyclic trimers or tetramers under suitable conditions. Progressively higher temperature is needed to initiate polymerization as the atomic weight of the halogen increases.

One of the unusual properties of $(\text{PNF}_2)_n$ is its low temperature elasticity which reflects a relatively high degree of torsional mobility of the chain. Of the three polymeric phosphazene halides, the fluoride has the lowest glass-transition temperature which is in accord with it having least inter-chain interaction and highest torsional freedom at low temperatures.

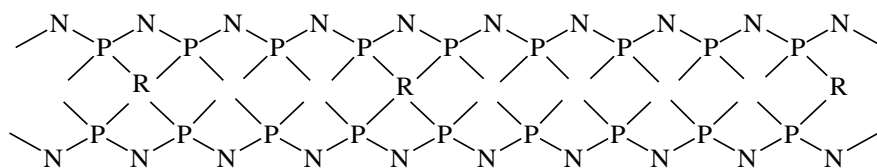
Poly bis isothiocyanophosphazene $[\text{PN}(\text{NCS})_2]_n$ can be made by direct polymerization of the cyclic trimer or tetramer. It is partially crystalline in the unstretched state and is a little more resistant to hydrolysis than the halide polymers.

Polymer properties are generally dependent upon such factors as chain-length distribution and inter-chain forces. The later may be strongly influenced by the nature of the side groups, moreover in some cases chemical reaction between these groups may lead to considerable cross linking taking place.

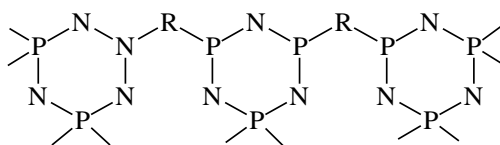
Although the polyhalophosphazenes have potentially useful physical and mechanical properties their chemical reactivity and hydrolytic instability rule out their practical use. Luckily however, an important aspect of the phosphazene polymer system is the relative ease with which the properties can be modified by the introduction of different side groups. Useful properties of such organopolyphosphazens include resistance to water, solvents, oils etc. non-inflammability and retardancy, stability to visible and ultra violet radiation, high thermal stability ($>200^\circ\text{C}$) low temperature flexibility and elasticity.



74(a)



74(b)



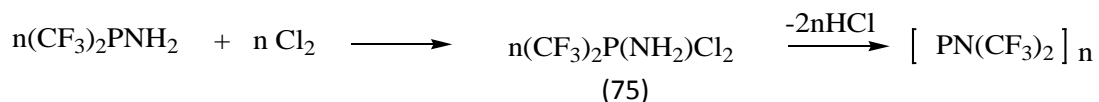
74(c)

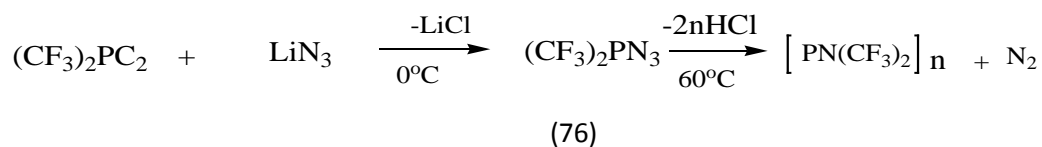
In addition to simple branching (74a) or cross linking (74b), more complex arrangements of the chains are known in which the phosphazene ring is retained as the basic structural unit. Polymers of this latter kind which are possible with halogen-substituted derivatives are known as cycloliner (74c).

Cycloliner polymers have been evolved with the aim of combining the thermal stability of the phosphazene ring with the flexibility or elastic properties of the chain which links them. On the other hand, cyclomatrix polymers contain fully cross-linked rings which are rigid, insoluble, higher melting point resins of a thermosetting nature.

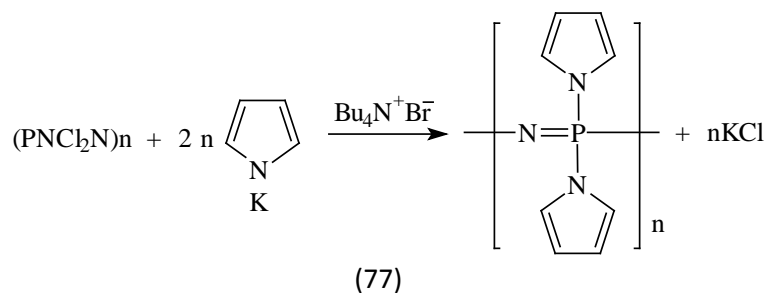
Polyorganophosphazenes often cannot be made by direct polymerization⁸¹ of the corresponding lower ring compound owing to thermal decomposition or other reactions taking place. More usually, substitution of the (uncross linked) polymerized halide is carried out. Polyalkoxy derivatives are e.g. made by treatment of soluble polymeric chloride with sodium alkoxide.

Polyorganophosphazenes are generally more stable to hydrolysis and often more heat resistant than the halides. The waxy $[(CF_3)_2PN]_n$ is stable to boiling concentrated acids and does not decompose below 380°C. This polymer is made by chlorination of bis (perfluoroalkyl) phosphorus amide followed by dehydrohalogenation of the product (75) alternatively it can be obtained from lithium azide according to equation (76).

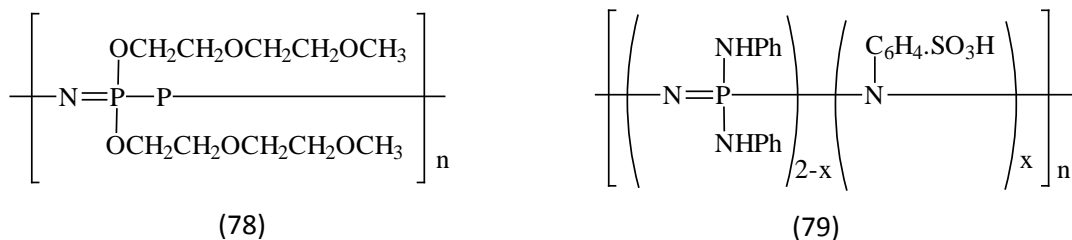




Polyphosphazenes containing CF_3 , CF_2 - and $\text{HCF}_2(\text{CF}_2)_n \text{CH}_2\text{-O-}$ groups retain their flexibility over large temperature ranges and as such have found application in braking systems of high performance aircraft.

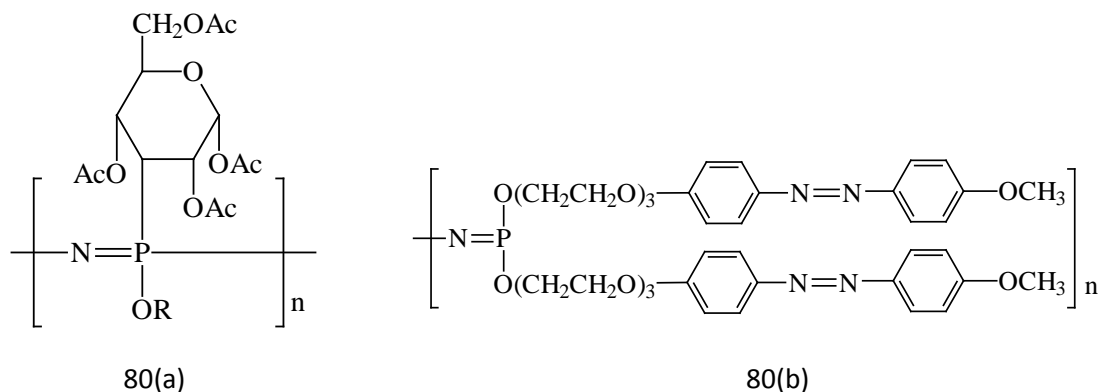


In general polyphosphazenes are electrical insulators but electronic semi-conducting varieties have been obtained. These include poly bis (pyrrolyl) phosphazenes (79).

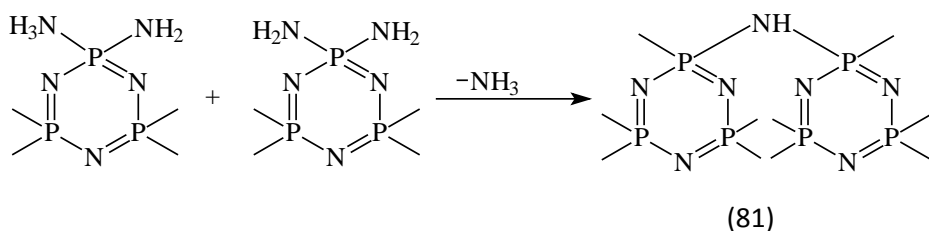


Polyphosphazenes such as (79) from amorphous solvent-free complexes with various salts. These are polymer electrolytes which have potential application in batteries, ion sensors, electrochromic displays etc.

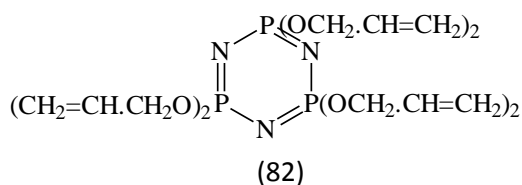
Glucose-substituted Polyphosphazenes⁶⁹ such as 80(a) also lead to water soluble products with potential biomedical applications. The fact that aromatic azo groups can be successfully introduced into the polymer side chains as in 80(b) suggests that such materials may prove to be the precursors of a new class of azo polymer dyestuffs.⁷⁰⁻⁷¹



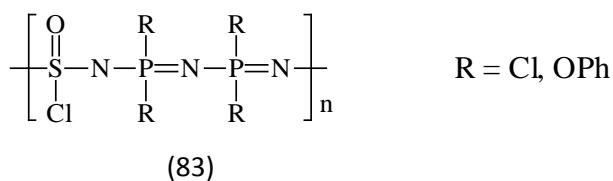
Aminocyclophosphazenes $[PN(NH_2)_2]_n$ where $n=3$ or 4 pyrolyse with the elimination of ammonia to give phosphams $(PN.NH)_n$. These are insoluble infusible amorphous grey-white solids which on further heating give phosphorus nitrides (81). Phosphams produced in this manner are believed to be cyclomatrix polymers containing trimeric or tetrameric rings randomly linked by NH bridges into continuous three-dimensional arrays.

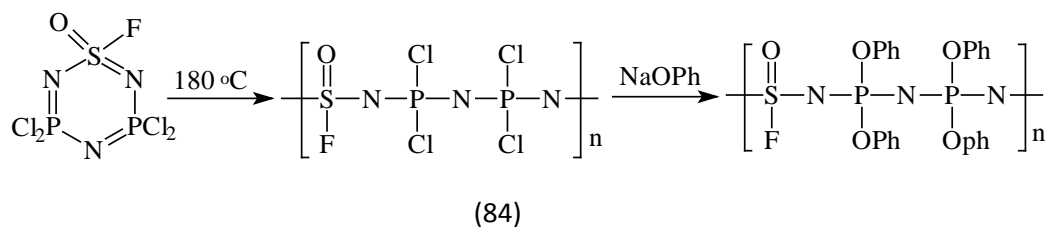


Rigid three-dimensional insoluble high-melting point resins can be obtained by polymerization of allyl derivatives such as (82).

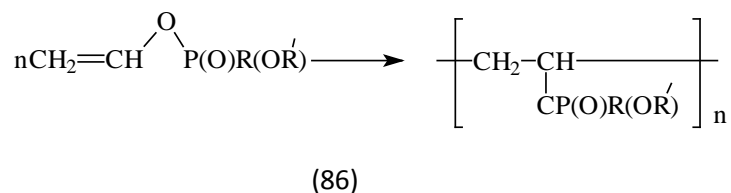
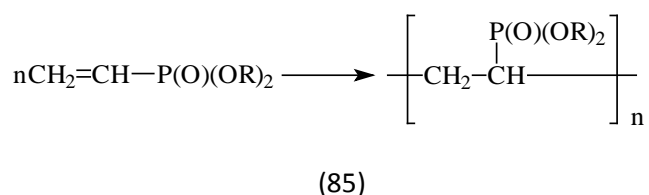


Sulphur-containing polyphosphazenes have been prepared but most of these, although elastomeric are moisture sensitive (83).

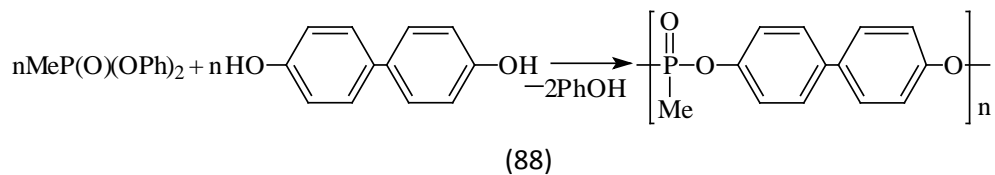
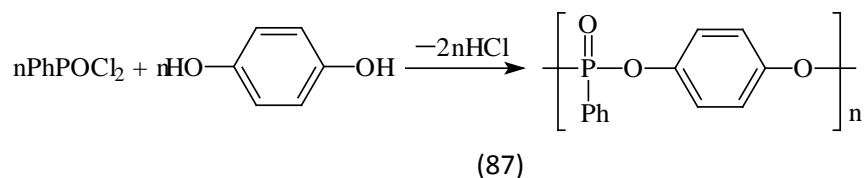


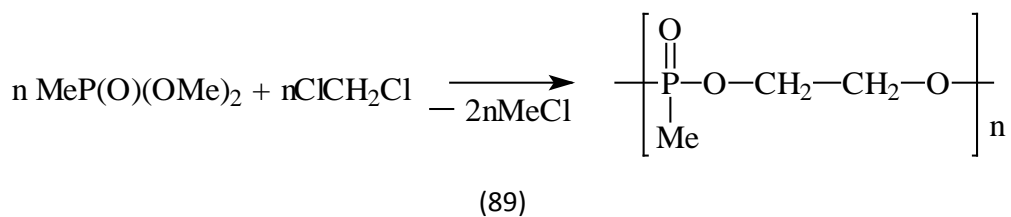


Polymerized phosphates constitute the most studied group of organophosphorus polymers, although in some cases the P-C linkages may be confined to the side chains. Among the methods which have been used for homopolymer formation are the heating of vinyl or allyl phosphonates (85) or vinyl or allyl esters of phosphonic acids (86).

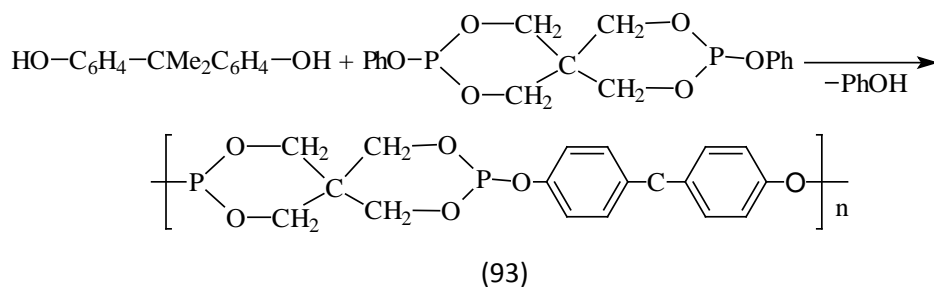
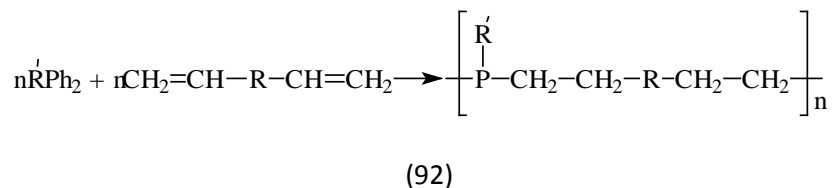
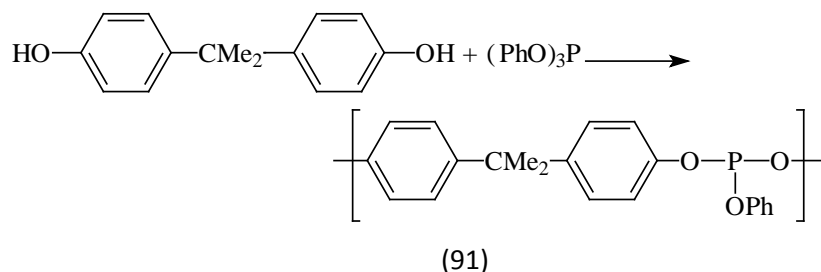
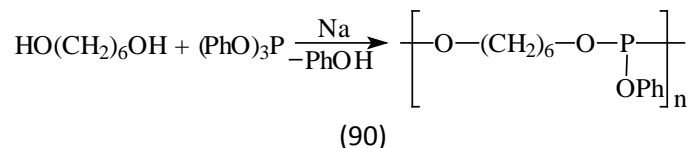


Methods used to obtain phosphonate co-polymers include transesterification reactions between suitable diols and phosphonyl dichlorides (87) or phosphonate esters (88) or reaction of the latter with dihalides (89).

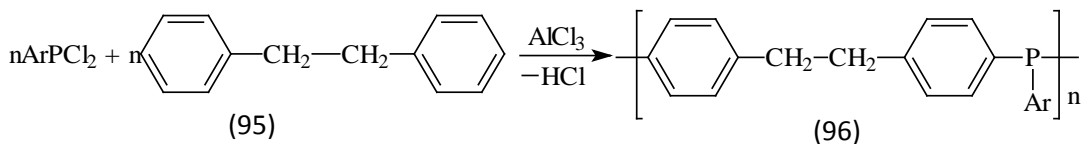
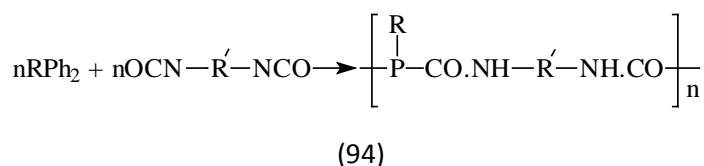




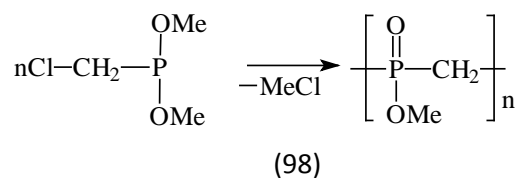
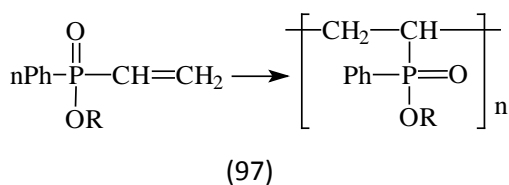
A limited number of polymerised phosphites have been made by reactions between phenyl phosphites and various diols. Typical examples of copolymers are;



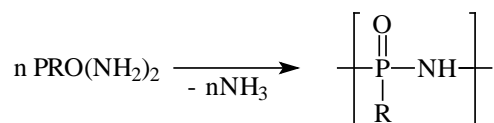
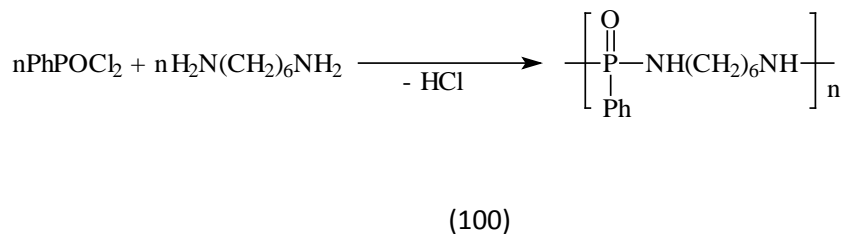
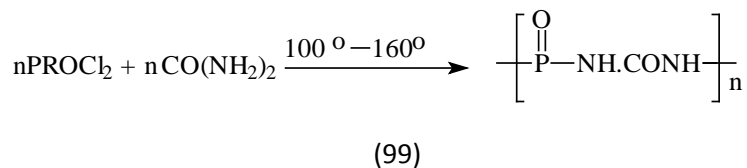
Phosphine copolymers can be obtained by heating primary phosphines with non-conjugated dienes (94) or condensing them with diisocyanates (95) or by reacting aryl phosphonous dihalides with certain hydrocarbons (96).



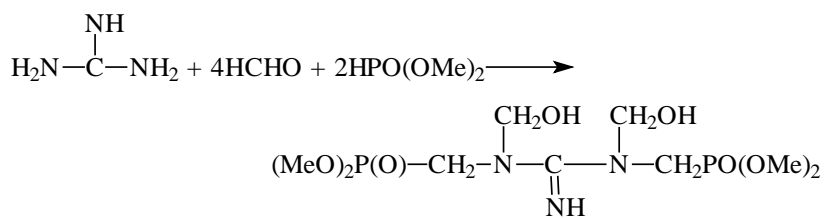
High molecular weight polyphosphinate homopolymers are obtained by heating phenyl (vinyl) phosphinic acid or its esters (97). When certain phosphinates are heated, an Arbusov rearrangement takes place, followed by condensation to give polymers with phosphorus in the main chain (98).



Polymers with either P-N (99) - (101) linkages in the main chain can result from reaction involving amides.

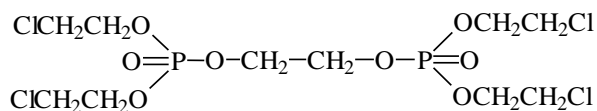


A permanent or semi-permanent fire resistance of paper, wood, plastics, fabrics etc. can be obtained when the fire retardant can be chem⁽¹⁰¹⁾ bonded to or physically incorporated in an insoluble form in these highly polymeric materials. In the case of synthetic materials, the most intimate bonding is usually obtained by co-polymerization with a fire retardant monomer or short-chain oligomer. Alternatively, it may be possible to attach the phosphorus compound by a suitable reaction with the preformed polymer. There are now several hundred organophosphorus or organic phosphate fire retardants are available for application. Although most of these are considerably more expensive than ammonium phosphate their use is often commercially justified particularly with high quality fabrics. Their mode of action in many cases is probably at least partially similar to that of ammonium phosphate. Flame and grease resistance can be imparted to cotton fibers by carrying out reaction (102) in their presence but there is some loss of strength.

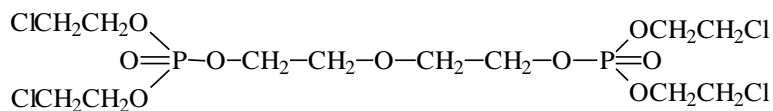


(102)

Two other commercial organic phosphates of the additive type are ‘Thermolin 101’ (103a) and ‘phosgard 1227’ (103b).

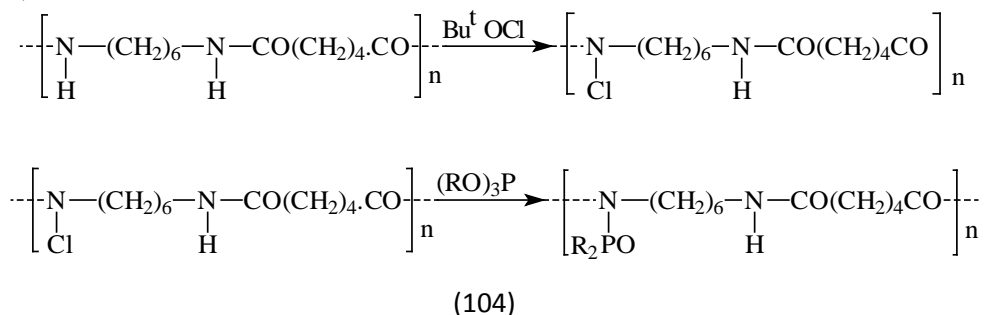


103(a)



103(b)

Nylon can be rendered flameproof by the part-replacement of imino H atom with phosphinyl groups. This is done by chlorination with t-butylpochlorite followed by treatment with trialkyl phosphate (104).



8. Detergents

Application of phosphorous containing synthetic material or synthetic detergent⁷² has many considerable advantages. Modern detergent powders combine moderate amounts of polyphosphates (sodium triphosphate in particular) with small amounts of organic surfactants. Introduced about 50 years ago, these powders have made a considerable impact and have replaced traditional cleaning materials such as soap and soda in many applications. The high charge on polyphosphate chain helps to stabilize detergent micelles. The sodium salt $\text{Na}_5\text{P}_3\text{O}_{10}$ is much used as a detergent builder in this way. Builders generally lower the critical micelle concentration and because many small micelles clean more effectively cleaning power. The triphosphate salt also acts as a sequestering agent and soluble triphosphate salt complex are generally more stable than those formed with pyrophosphate. The most popular form of solid detergents is a characteristically hollow puffed particle (diameter $\sim 2\text{mm}$, $\rho = 0.35 \text{ g/cc}$ which because of its high surface area is rapidly soluble under washing conditions aqueous slurry containing most of the components. Processing time and other conditions adjusted to minimize hydrolysis of the triphosphate. Some items very unstable under spraying conditions e.g. sodium perborate, perfume or proteolytic enzymes have to be incorporated later by mechanical mixing. Liquid detergent formulations are the most suitable and convenient moreover they remove the need for dry blending equipment in manufacture. They detergents are usually based upon potassium salts because of their much greater water solubility than that of the sodium salts. Pyrophosphates, although not quite as efficient as triphosphates are preferred to the later because of their greater resistance to hydrolysis during storage.

9. Metal surface treatment

Phosphorus containing compounds are also used in metal surface treatment⁷³. Present day application is mostly to steel and zinc (galvanized steel) products although iron, aluminium, tin and cadmium may also be successfully treated.

Principal advantages obtainable from phosphating treatments are:

- (1) rust proofing
- (2) improved paint adhesion
- (3) increase wear resistance
- (4) easier cold working

Phosphating may be carried out by (a) immersion, (b) spraying or (c) brush application the first method usually being the most effective and now the most widely used.

Organophosphorus compounds or other organic compounds are included in many modern patented phosphating composition, these compounds are variously cited as complexing agents, activators, crystal refiners, pre-conditioners, accelerators, surface active agents, cleaners etc. The resulting coating compositions are often less well defined than those obtained with more traditional phosphating recipes, although superior results are usually claimed. Some of these processes involve the formation of coatings in which the metal atoms are chemically bound to both phosphate groups and organic ligands.

10. Glasses

Glass industry has phosphorus containing compounds used as phosphate glass⁷⁴. Phosphate glasses can be prepared over a wide range of composition. The glasses formed with Na⁺ cations have been examined most thoroughly and these exist in a continuous series, stable at normal temperatures, from the composition P₂O₅ up to about 5Na₂O. P₂O₅. Knowledge of the structure of such glasses is far from complete but present evidence indicates they proportions depending upon the Na₂O/P₂O₅ ratio.

11. Cements, refractoriness and constructional materials

Phosphate cements because of their relatively high cost, can never be considered as bulk building materials which could compete with Portland cement or even high alumina cement. They do however have important uses where relatively small quantities are needed as e.g. dental cements⁷⁵, electrically insulating cements, as bonding agents in refractory materials or in certain specialized building materials. In other ceramic materials where phosphorus is not intentional component, the element is usually present as a trace impurity quantity. Phosphates have not so far found much application as refractory materials in their own right. Aluminium orthophosphate (AlPO_4) would be a good refractory material it not for the fact that loss of P_2O_5 occurs above about 1100°C and this becomes serious above 1500°C .

Calcium metaphosphate can be bonded into sheets with relatively minor quantities of glass, PVC, rayon, polyester, graphite etc. The patent literature contains numerous recipes for constructional materials which utilize phosphogypsum the waste product from superphosphate manufacture. Phosphogypsum can be combined with phenol-formaldehyde resins cotton and flax wastes to give high-strength building materials.

12. Dental and medical materials

Di-calcium phosphate dihydrate, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ was introduced into toothpaste over 50 years ago as a mild abrasive and polishing agent to replace calcium carbonate. The humectants prevent dehydration of the dicalcium phosphate dihydrate to the anhydrous form which is too abrasive. Insoluble forms of sodium polyphosphate are compatible with fluorides and have been used as toothpaste abrasive. Peroxy di-phosphates have also been used. Sodium acid pyrophosphate and potassium pyrophosphate are included in some formulations as anti-tartar. Phosphate ester has been patented as dental⁷⁵ adhesives.

Bone substitutes for dental or pediatric use can be made from tri-calcium phosphate, hydroxyphosphatite or other P_2O_5^- containing compounds. In some cases strengths can be made to exceed that of bone although the synthetic products are usually more brittle than the latter.

These materials include sintered crystalline products, glasses and glass-ceramics all of which can be fabricated with adequate strengths. They compatible with bone tissue to which in most cases

they become chemically bonded, limited surface dissolution combined with precipitation at the interface may be involved. Additional bonding by mechanical interlock may take place with the more porous product, although the latter generally have lower strengths. Hydroxyapatite is not as strong as alumina but adhesion of the latter to bone is poor.

Hydroxyapatite has emerged as generally the most satisfactory bioceramic materials for surgical implant work. This is because it

- a) has adequate strength
- b) shows no foreign body reaction
- c) bonds strongly to bone
- d) does not dissolve or corrode
- e) is non-toxic
- f) has good fatigue resistance when pore structure is minimal.

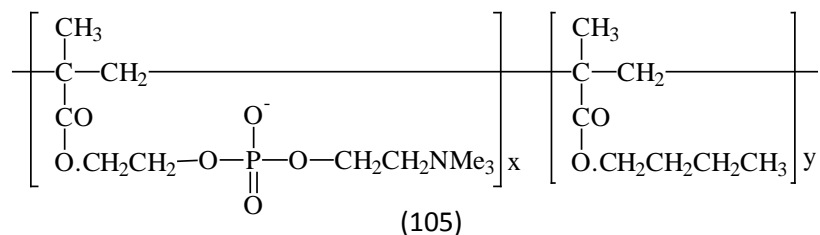
Synthetic materials based on hydroxyapatite are used as implants in ear, nose and throat surgery, facial and cranial rebuilding and in fracture healing. Dental uses include crown, tooth capping, dentures and tooth implants.

Artificial bone can be made using suitably ground hydroxyapatite or some of the glass ceramic compositions as fillers in plastic materials such as polyethylene or polymethacrylate. Furthermore, it is claimed that by heating composite materials of this type to 1100°C, most of the organic components can be burnt off; leaving a high porosity inorganic material if it is desired.

Biocompatible high-strength ceramics have recently been obtained from hot pressed mixtures of hydroxyapatite and zirconia. Sintered composites are reported to have excellent fatigue resistance.

Protein adsorption on biomedical materials is important in determining their blood compatibility. New hemocompatible and non thrombogenic polymers have recently been evolved on which surface layers are formed to give minimal interaction with cells and proteins. These are copolymers of methacrylates and phospholipid derivatives.

MW~10⁵



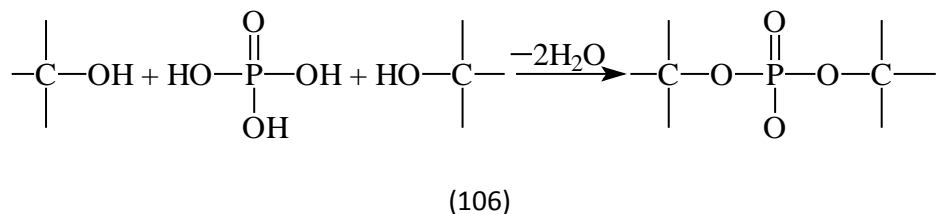
Materials for dental and bone implants, based on calcium phosphate/chitosan complexes have recently been patented.

Artificial bone or teeth can be coated with phosphate glass or hydroxyapatite layers. Biodegradable glass has been prescribed for use as implants in surgical techniques and water-soluble glasses for temporary post-operative support of bone and tissue have been patented. Porous bone cements or implant materials based on hydroxyapatite or tri-calcium phosphate can be impregnated with antibiotics or growth hormones.

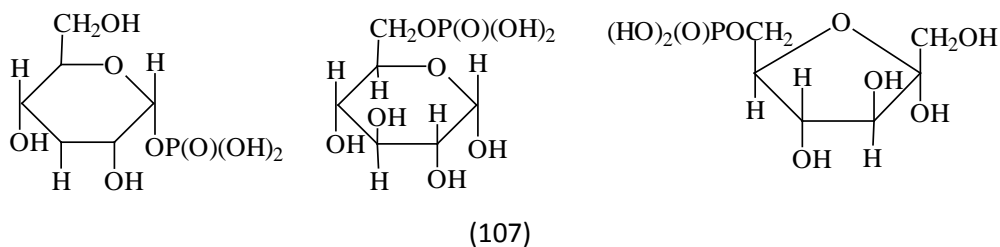
13. In natural products

Natural products in the form of biopolymers⁷⁶⁻⁷⁸ are very much important as these are mostly phosphorus containing organic compounds. All nucleic acids are phosphate esters, only some varieties of proteins, lipids, polysaccharides are found in phosphorylated form and these may be termed phosphoproteins, phospholipids and phosphosaccharides respectively. Phosphorylated forms are intimately involved in the function of the all-important type of proteins known as enzymes.

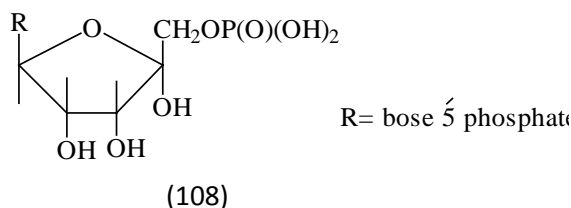
The four types of biopolymer are frequently encountered in nature as intimately linked of considerable complexity. These associated units are known as lipoproteins, glycoproteins, proteoglycans, glycolipids, nucleoproteins etc. Phosphate groups when present in either biopolymer may also act as bridging groups.



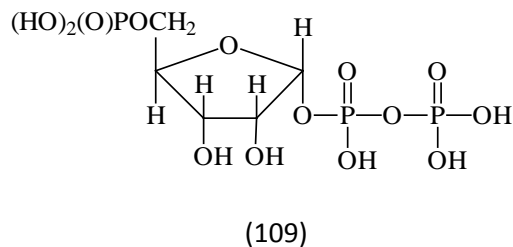
The monosaccharide found in living system is mostly mono and di-phosphate esters. Of the greatest importance in animal metabolism are the three esters (107) which also occur in plant life, particularly fruit. They have high water solubility and high acid strengths. Individual glucose phosphates vary greatly in their hydrolytic behavior.



Amongst the ribose phosphates, ribose-5-phosphate (108) is utilized in forming the all important nucleotides.



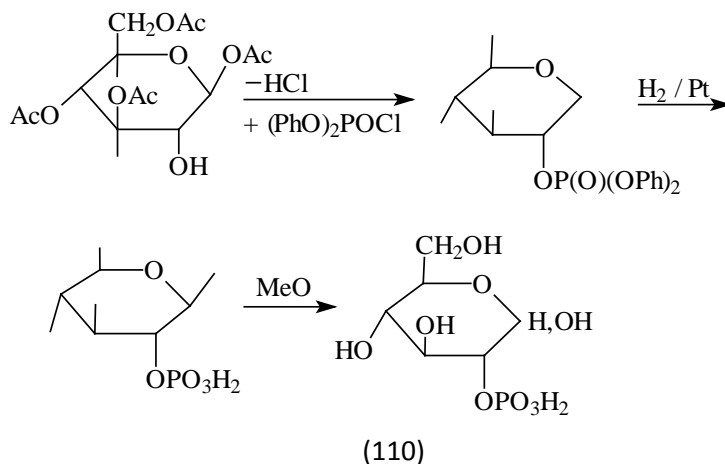
An important compound in biochemistry is 5-Phosphoribosyl-1-pyrophosphate (PRPP) (109). This compound is involved in the biosynthesis of amino acids and NAD.



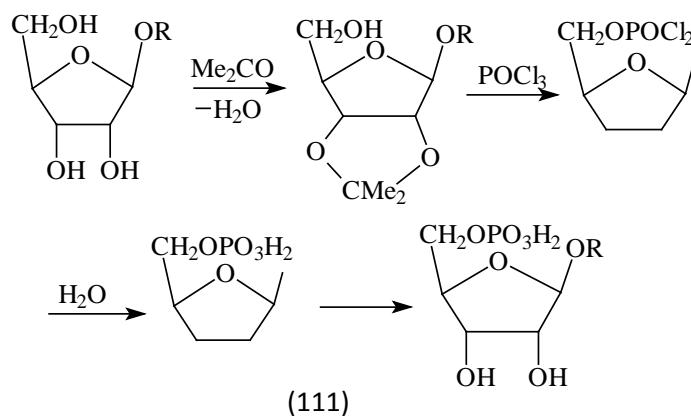
Saccharide phosphate esters can be isolated from natural sources or produced by chemical synthesis. Fructose-1,6-diphosphate can be isolated from yeast and glucose-1-phosphate can

be obtained by phosphorolysis of glycogen. For preparation of bulk quantities, chemical methods of synthesis are usually to be preferred although they are not always available. As a result of studies over the past few decades, a wide variety of suitable phosphorylating agents have become available for treating both simple sugars and nucleotides⁶⁵⁻⁶⁷. The most widely used phosphorylating agents diphenyl phosphorochloridate $(\text{PhO})_2\text{POCl}$ and dibenzyl phosphorochloridate $(\text{PhCH}_2\text{O})_2\text{POCl}$ are normally used in pyridine solution.

Simple monosaccharides such as D-glucose – 6 – phosphate can be prepared by direct phosphorylation of the unprotected sugar. In general, however the sugar -OH groups have to be protected while phosphorylation can be carried out at the desired position and the protective groups afterwards to be removed. Glucose –2– phosphate can be formed as;



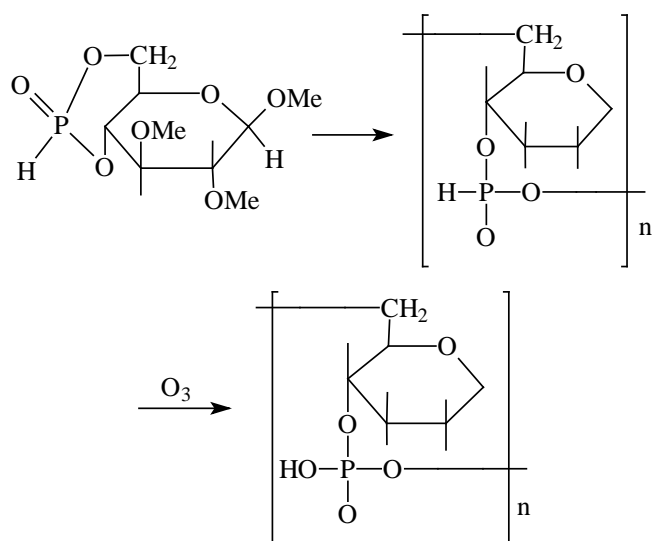
In some cases phosphoryl chloride is a satisfactory phosphorylating agent as;



Polysaccharides are widely distributed in plants and animals. They are present both as structural materials as in cellulose and as food storage compound such as starch and glycogen. Phosphorylated polysaccharides, phosphorylation with consequent modification of properties is possible in principle for any polysaccharide. Phosphopolysaccharides (Polysaccharide phosphate esters) of this kind occur frequently in living systems and in a number of important technological products. Many bacterial polysaccharides contain phosphate ester groups these include the teichoic acids.

A considerable number of phosphosaccharides have been characterized by NMR, mass spectra, chromatography or other techniques. Many of these phosphosaccharides have however been obtained only in minimal amounts via biochemical processes and satisfactory chemical means for their bulk preparation are not yet available.

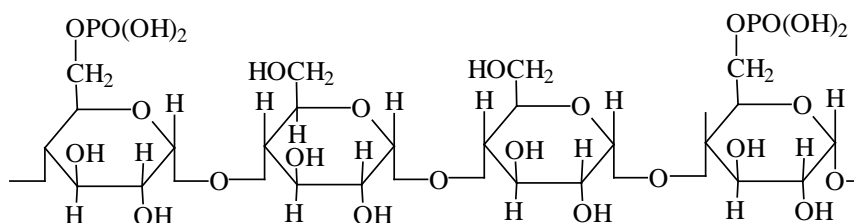
In sugar-phosphate chains⁷⁹ consisting of sugar rings alternating with phosphate groups can be obtained by entirely synthetic methods. Ring opening has been shown to yield high molecular weight polymers.



(112)

Polymer chains consisting of alternating sugar rings and phosphate groups are found in nucleic acids and in some varieties of teichoic acids.

Reaction of cellulose with concentrated phosphoric acid or phosphoryl chloride, results in the replacement of a few of the -OH groups by OP(O)(OH)_2 groups (113).



(113)

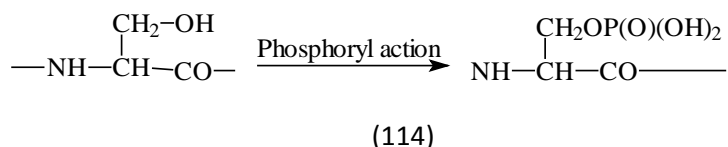
Phosphorylation at the C_6 atom is usually assumed, although other carbon atoms may also be involved in a more or less random manner.

An increased flame-resistance can be obtained with phosphorylated cellulose but at the expense of partial degradation and loss of fiber strength and increased water solubility. Cellulose phosphate salts are useful as cation exchange resins in protein chromatography and for peptide separation. Amongst the biological polymers, proteins⁷⁹⁻⁸⁵ have the most diverse functions and are in fact the most complicated substances known to science thousands of different varieties exist in every living organism.

Animals generally contain about ten times more protein than plants. All proteins are built from carbon, hydrogen, oxygen, nitrogen and usually some sulphur. The pure protein structures are devoid of phosphorus. Phosphoproteins only result when appropriate substitution is made. Proteins are usually of two types conjugated proteins and non-conjugated proteins. Proteins often occur naturally in close association with other biopolymers and such combinations are sometimes known as conjugated proteins. They include nucleoproteins, lipoproteins and glycoproteins. Either or both components of a conjugated protein may be phosphorylated. In the case of nucleoproteins, phosphorus is always present in the nucleic acid component. Some may prefer the prefix 'phospho' to be used to signify which component is phosphorylated e.g. phospholipoprotein or lipophosphoprotein. More than a hundred different phosphoproteins have

now been recognized. The best known of these include milk casein, the egg proteins- phosvitin and ovalbumin and the iron-storage protein ferritin.

Phosphorylation of proteins nearly always occurs on serine residues (114) but threonine, tyrosine, histidine and lysine can also be involved.



Many enzymes are phosphoproteins⁸⁶⁻⁹⁰ and enzyme action is frequently associated with phosphorylation dephosphorylation of the protein residues particularly in serine.

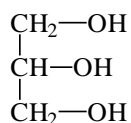
Phosphorylation replaces – OH with – OP (O) (OH)₂ and places a negative charge on the protein. Interference with the existing hydrogen bonding scheme and the introduction of a relatively large phosphate group can generally be expected to modify the secondary and tertiary structure of protein.

Protein phosphorylation is involved in numerous biochemical processes. These include the regulation of metabolic pathways, membrane transport, muscle contraction, hormone response, photosynthesis, cell division, gene transcription and translation and brain processes such as learning and memory.

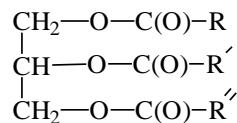
Phosphoproteins can be extracted from bone and dentine with EDTA. The phosphoproteins in dentine form about 10 % of the total protein present and have a very high serine and aspartine content with about half of the serine residues phosphorylated. Isolated phosphoprotein has been shown to catalyze the formation of apatite from amorphous tri-calcium phosphate and it may act in this way in teeth⁷⁸. Casein is the most abundant protein in milk which consists of four phosphoproteins (•_{s1}, •_{s2}, •, •) which occur in close association with calcium phosphate in the form of micelles.

Lipids are water-insoluble, oily or greasy substances that can be extracted from cells and tissues by non-polar solvents. The most abundant kinds are fats which are triglycerides and they act as

major storage fuels in most organisms. Triglycerides are fatty acid esters of glycerol (115a) with general formula (115b) where R, R', R'' are long hydrocarbon chains of composition $(\text{CH}_2)_n$ methyl derived from fatty acids $\text{HOOC}(\text{CH}_2)_n\text{CH}_3$.



115(a)

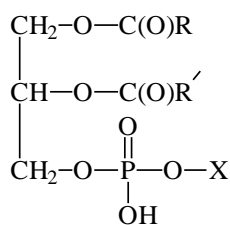


115(b)

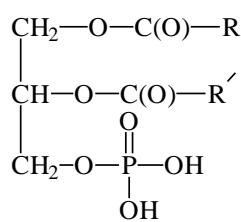
In addition to glycerolipids (115b) if the lipid contains one or more polar phosphate group, it is called a phospholipid.

Phospholipids are major components of cell membranes and occurs widely in bacteria, animal and plant tissues. They are involved in enzyme action and transport of tri-glycerides through the liver and they have a role in electron transport and oxidative phosphorylation.

The most important commercial source of phospholipid is lecithin which has numerous food and nonfood applications. The properties of starch and bread are modified by their small phospholipid content. The most abundant phospholipids are those with the general formula where R is a long chain fatty-acid residue and X can be various groups. They are derivatives of glycerophosphoric acid and are sometimes called glycerophospholipids.



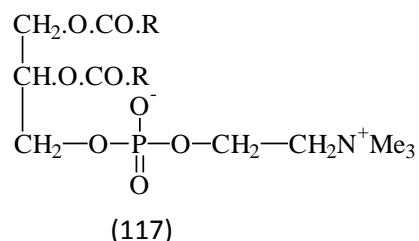
116(a)



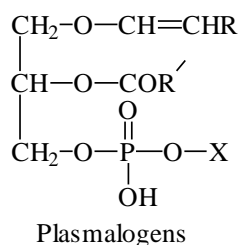
116(b)

When X=H, these compounds are the parent phosphatidic acids 116(b). In naturally occurring phosphoglycerides 116(a), X is most frequently choline, ethanolamine, L-serine

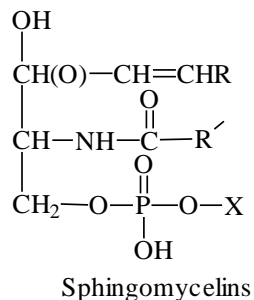
or inositol and R is a mixture, the principal components of which are palmitic and oleic together with smaller quantities of other long-chain residues. Lecithin (117) is found in egg yolk, brain tissue and in skin. It exists as zwitterions in its physiological environment.



Most phospholipids are water soluble as well as fat soluble because their molecules have hydrophobic as well as hydrophilic regions and are polar in character. So they are called amphiphatic lipids. In general, membrane lipids are amphiphatic phosphoesters whereas storage lipids are not. Phospholipids are important for their emulsifying properties. In an oil water system the molecules concentrate at the interfaces and lower the surface tension thus enabling droplets to be formed, they act as a barrier at the interfaces and stabilize the emulsion. When heated with acids or bases most phosphoglycerides are split into their components i.e. fatty acids, glycerol, phosphoric acid and the base head group. Plasmalogens are phosphatidyl derivatives in which the fatty acid in the α -position has been replaced by an unsaturated ester (118 a). There are found in brain and nervous tissue.



118(a)

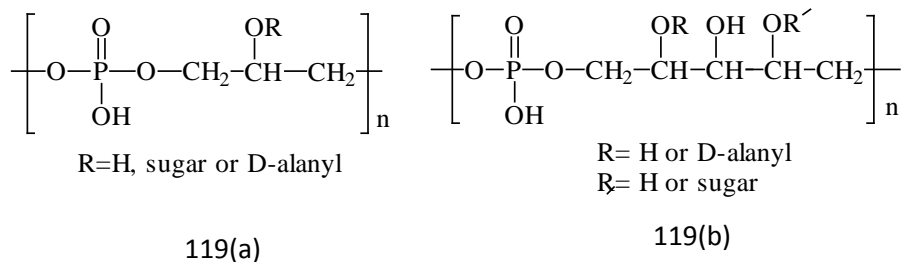


118(b)

Sphingomyelins are phosphorus containing members of the second large class of membrane lipids known as sphingolipids 118(b). The head group X is most commonly choline or ethanolamine and these compounds resemble the corresponding phosphatidyl compounds in their

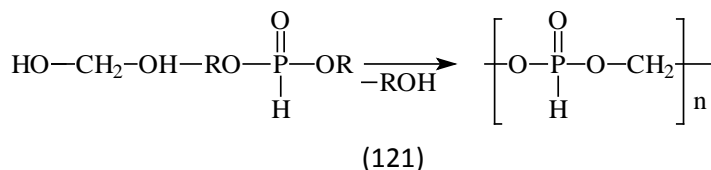
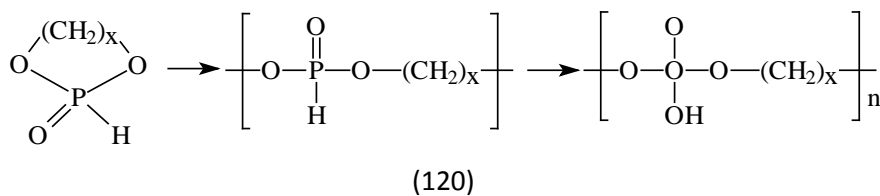
general properties. They are found in most animal membranes, particularly in the ‘myelin sheath’ surrounding certain nerve cells.

Some lipids are conjugated with proteins to form lipoproteins. Lipovitellin and lipovitellenin are phospholipoproteins. Blood contains various types of plasma lipoproteins which consist of triglycerides, proteins, phospholipids and cholesterol. These closely associated units may be covalently linked to each other in some cases. Phosphate groups, glycerol, ribitol and saccharide units are the basic components and the simpler derivatives can be represented by the formulae (119).



The simplest parent compound poly (glycerol phosphate) R=H in 119(a) has been prepared by laboratory methods, poly (ribitol phosphate) R=R'=H in 119(b) has been prepared by phosphorylation of 119(a).

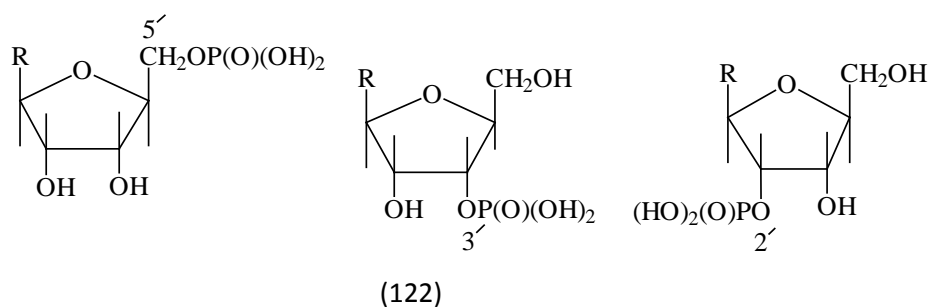
The polymer (alkylene phosphates) which can be made by ring opening polymerization (120) or by condensation of dialkyl phosphites (121). Molecular weights of over 10,000 have been achieved⁷¹.



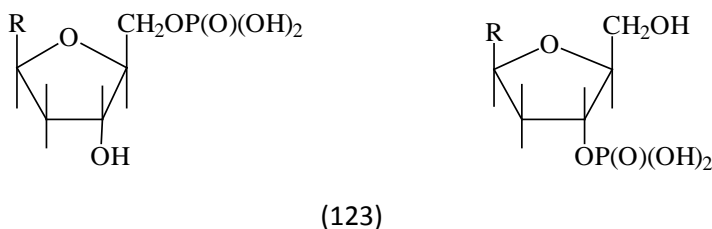
The nucleic acids are not only responsible for the storage and transmission between generations of genetic information but they also pass on this information to direct the synthesis of the proteins characteristic of the cell. Nucleic acids frequently occur in close association with proteins as nucleoproteins. Nucleic acids are closely associated with mononucleotides, modified polynucleotides and nucleotide phosphates. They all contain phosphorous, mononucleotide units are built from three main components, a phosphate group, a sugar-ribose or deoxy-ribose, a nitrogen base, a purine or a pyrimidine.

The mononucleotides (mononucleoside phosphates) are obtained by breaking down the polynucleotides or by phosphorylation of pre-formed nucleosides. Their main biochemical role is to function as sources of the nucleoside pyro and triphosphate.

Various isomers of mononucleotides are found. The ribonucleosides may be phosphorylated in the 2', 3' or 5' positions (122).

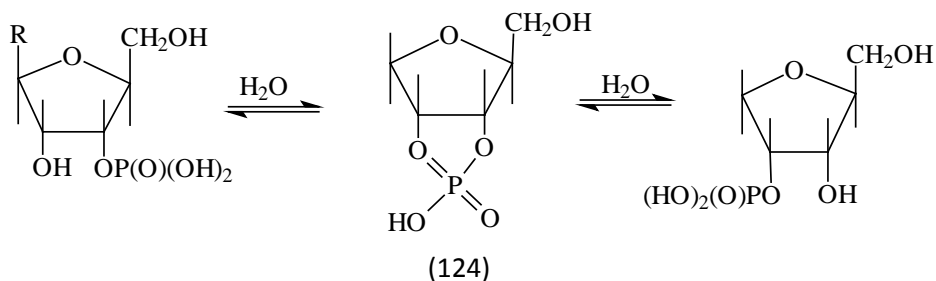


Whereas the deoxyribonucleosides may be phosphorylated only at 3' or 5' □ positions (123).

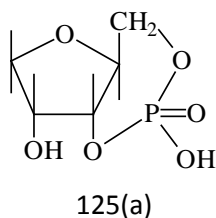


The 5'- ribonucleosides are strongly acidic. The ribo nucleic acid (RNA) mononucleotide unit containing adenine is adenosine -5'- monophosphate (AMP). This compound is the hydrolyzed product of adenosine tri-phosphate (ATP).

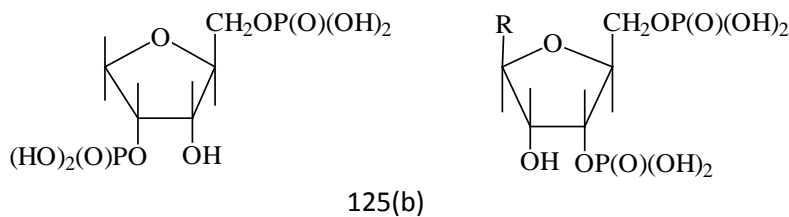
The ribonucleoside -2' and 3' phosphates are readily interconvertible in acid solution and this inter-conversion proceeds through the cyclic 2', 3'- phosphate (124).



Adenosine -3', 5'- mono-phosphate (Base = adenine) in 125(a) is of considerable importance in biochemistry. Hydrolysis of this compound with Ba (OH)₂ gives a mixture of adenosine -3'-phosphate and adenosine -5'- phosphate.



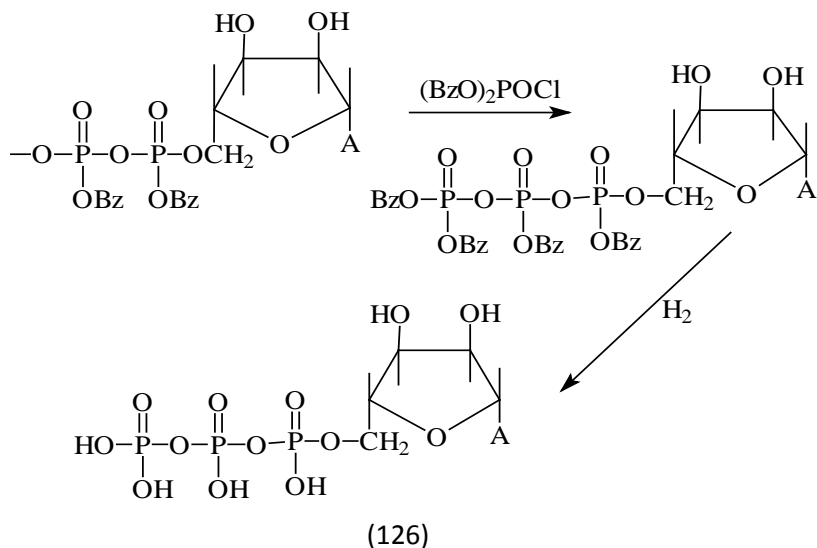
Nucleoside bis-phosphate 125(b) can be prepared and have considerable importance in biochemistry.



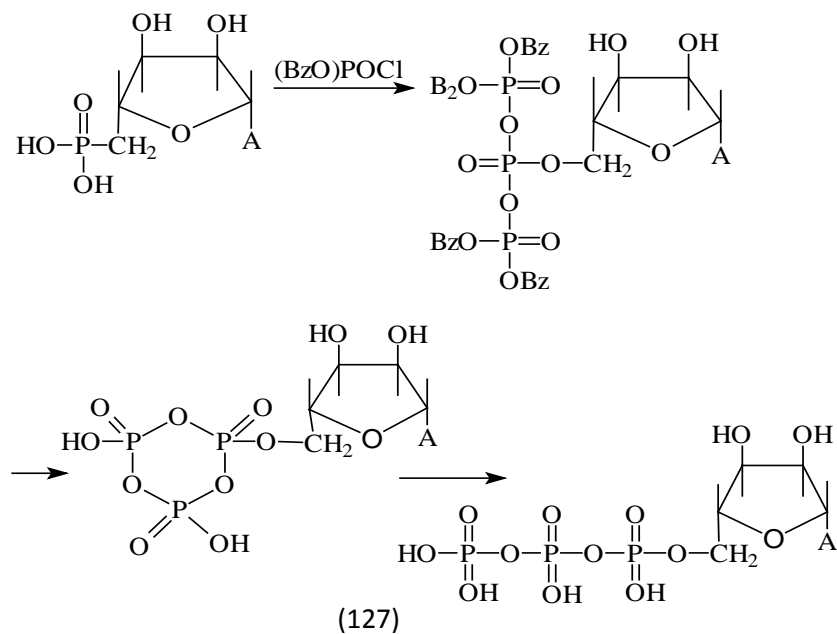
Although ATP was first discovered by Fiske and Subarrow⁹¹ in muscle in 1929 the first laboratory synthesis was achieved after 20 years by Todd as co-workers⁹².

In their first method, the silver salt of adenosine -5'- dibenzyl pyrophosphate was reacted with dibenzyl phosphorochloridate and this was followed by catalytic hydrogenolysis to remove the

benzyl groups. The pyrophosphate salt had been prepared by a similar route using di-benzyl phosphorochloridate and adenosine-5'-monophosphate.



In another synthesis, the di-silver salt of adenosine -5'- phosphate was treated directly with an excess of dibenzyl phosphorochloridate and this was followed by hydrogenolysis and hydrolysis as (127).



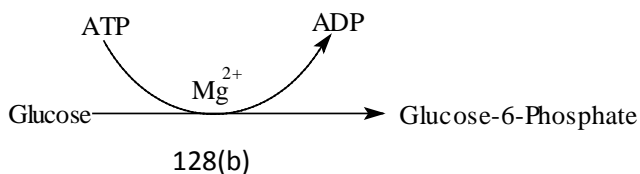
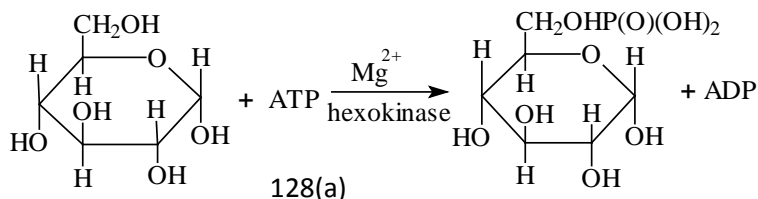
Almost all biochemical reactions are catalyzed by enzymes. Enzymes are a special kind of catalyst which are proteins and which are effective in extremely small concentrations. Enzymes are usually proteins, all enzymes contain nitrogen and most of the enzymes contain phosphorous. A very high proportion is involved with reactions of phosphate esters and phosphorus is often present in the cofactors.

Enzymes which catalyze hydrolysis are known as hydrolases and if the compounds acted upon (substrate) are esters they are known as esterases. If the action is specific to phosphate esters, these compounds are known as phosphoesterases or phosphatases.

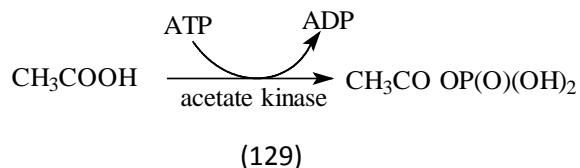
The enzymes which catalyze 'phosphate transfer' or phosphorylation is very important in biochemistry. These have been known variously as phosphotransferases, phosphorylases, phosphokinases, transphosphorylases etc.

There are two phosphorylation processes of fundamental importance of biochemistry. These are photophosphorylation the process by which green plants convert light energy to chemical energy. And the oxidative phosphorylation, the process by which a large part of the energy in foods is conserved and made available to the cell.

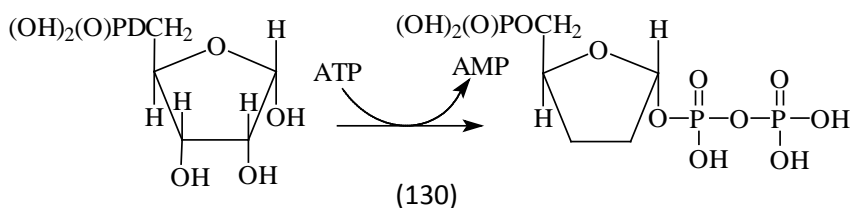
Adenosine tri-phosphate (ATP) phosphorylates glucose as it enters the living cell according to reaction 128(a) which can alternatively be written as 128(b). In this non-reversible reaction in which ATP act as the phosphorylating agent, the enzyme is given a special name hexokinase. Enzymes which catalyze transfers specially to and from ATP are sometimes called phosphokinases.



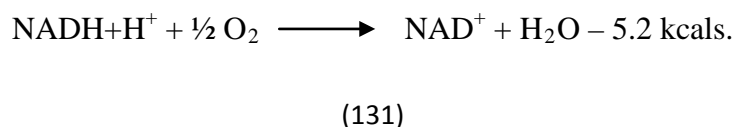
Another example is provided by the phosphorylation of acetic acid (substrate) to form acetyl phosphate which is catalyzed by the phosphokinase enzyme known as acetate kinase (129). This reaction can occur in reverse in which case the acetyl phosphate is said to phosphorylate the ADP to ATP. Both di-phosphate and tri-phosphate esters can act as phosphorylating agents.



Enzymes which catalyze the transfer of a pyrophosphate group are sometimes known as pyrophosphorylases, although ATP normally functions as a phosphorylating agent, it will sometimes act as a pyrophosphorylating agent as in the conversion of ribose -5- phosphate to a •-5-phosphoribosyl-1-pyrophosphate (130).



Oxidative phosphorylation occurs in the formation of ATP from ADP when it is coupled to the process of electron transfer from NADH or FADH₂ to oxygen (131). This occurs in the terminal oxidation of glucose. Electron transport and oxidative phosphorylation take place in nearly all types of aerobic cell.



Photophosphorylation occurs when ADP is converted to ATP during the complex process of photosynthesis. Protein phosphorylation⁷⁵⁻⁸⁶ is one of the important phenomena of the living cells. Phosphorylation is one of the chief mechanisms whereby cells can rapidly activate or

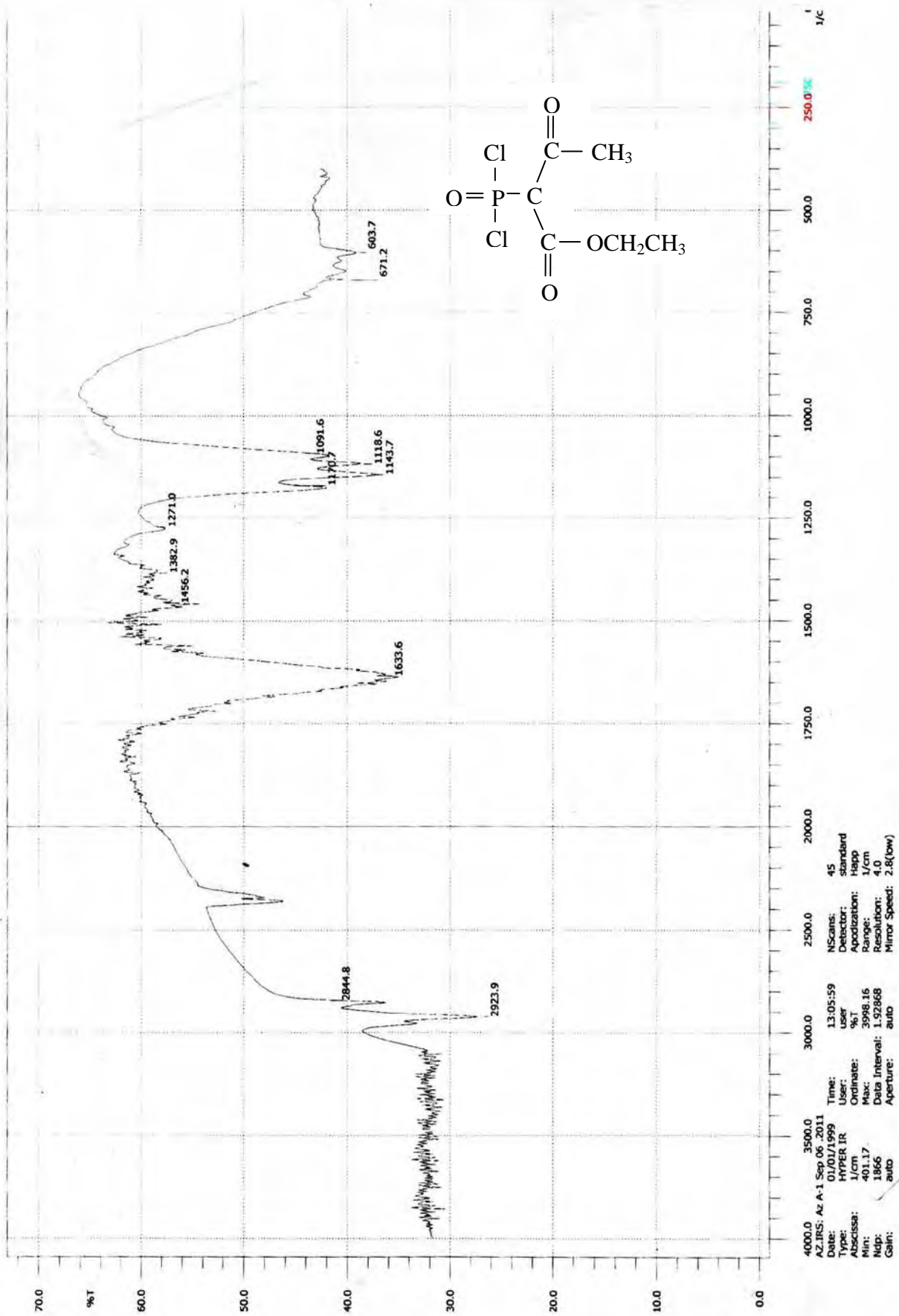


Fig. 1a: IR Spectrum of Compound 1A.

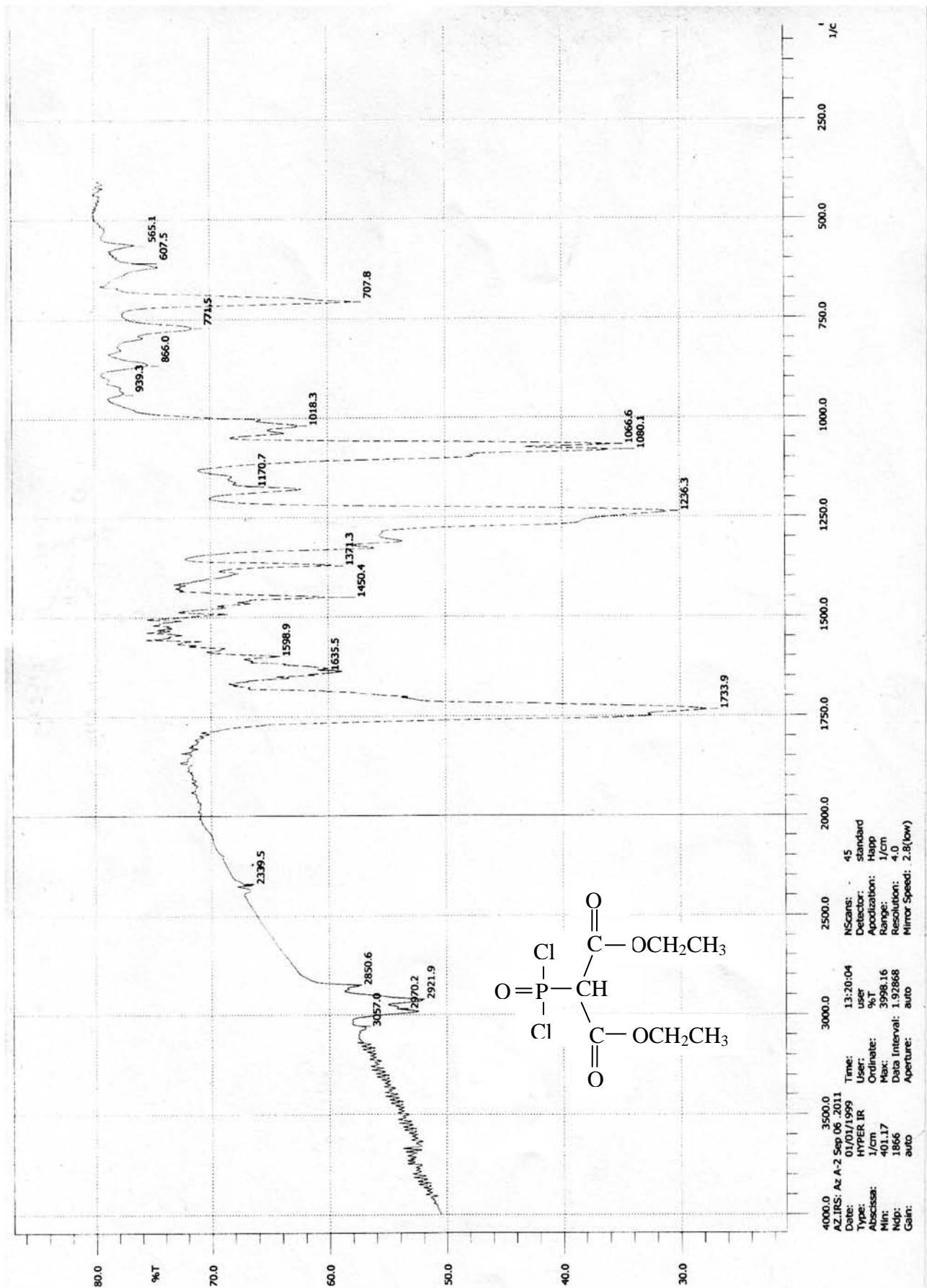


Fig. 2a: IR Spectrum of Compound 2A

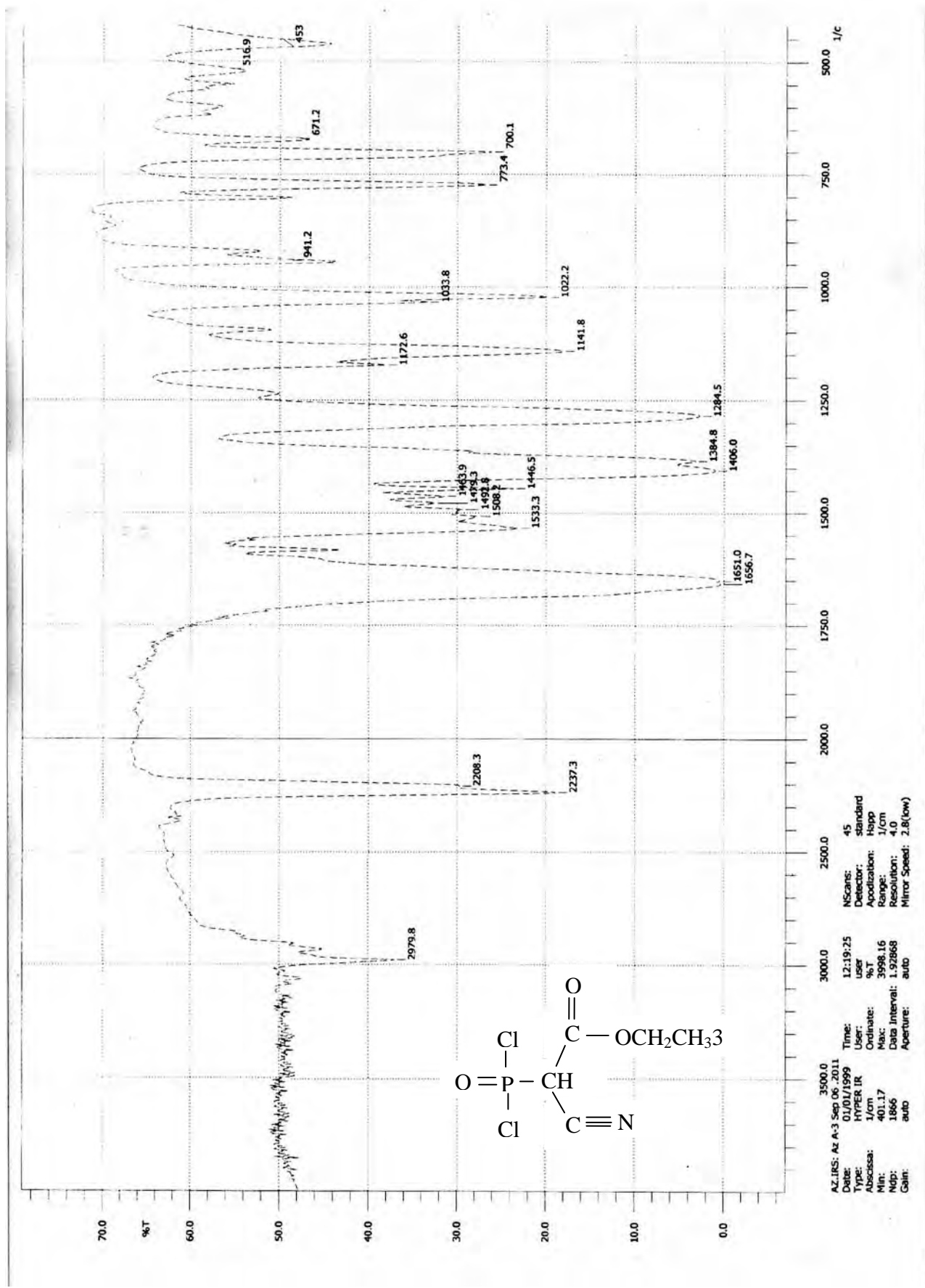


Fig. 3a: IR Spectrum of Compound 3A.

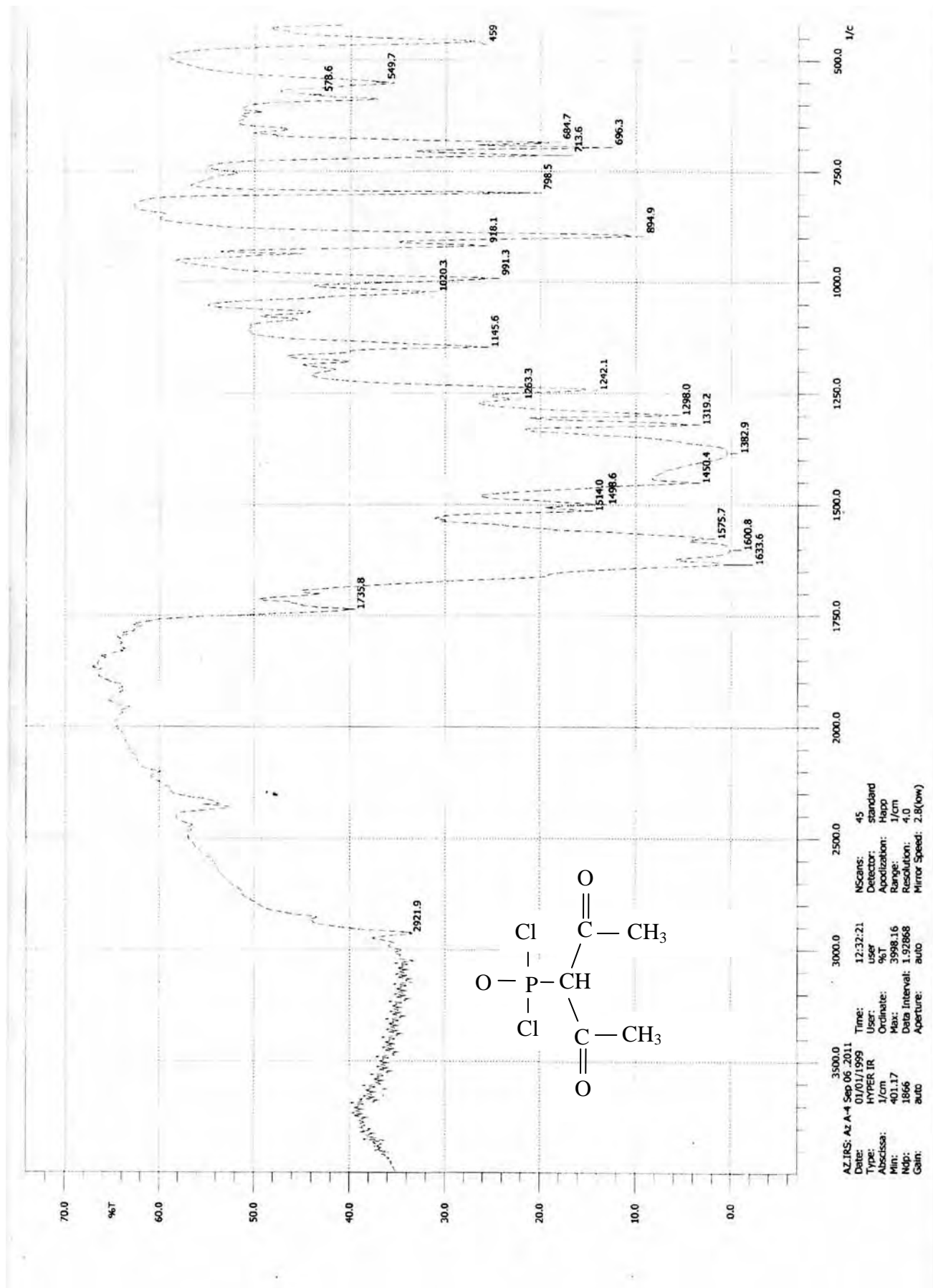


Fig. 4a : IR Spectrum of Compound 4A.

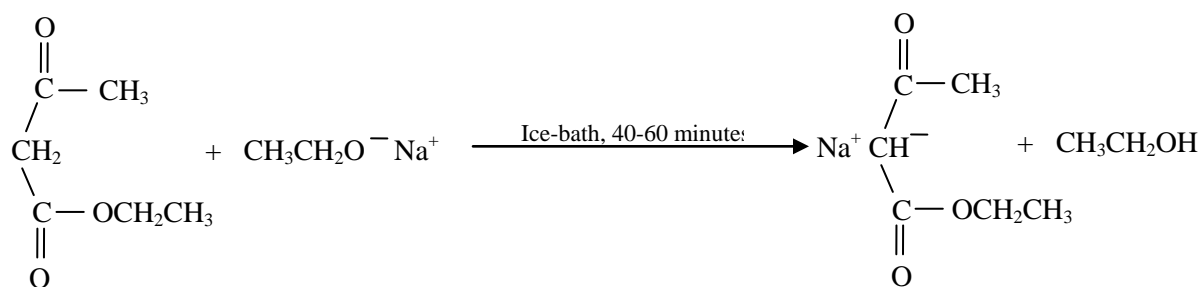
2.7. Mechanism of Synthesis:

Synthesis of phosphine oxide by using active methylene compounds as starting materials involve the following steps:

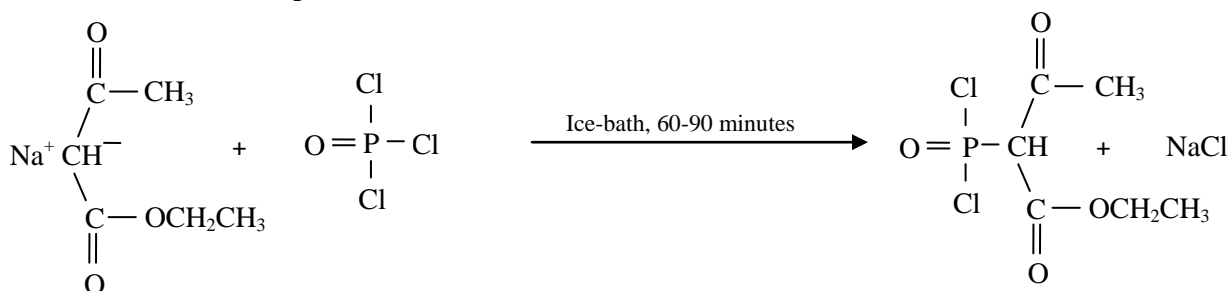
Step 1: Sodium metal reacts with absolute ethanol to sodium ethoxide at room temperature.



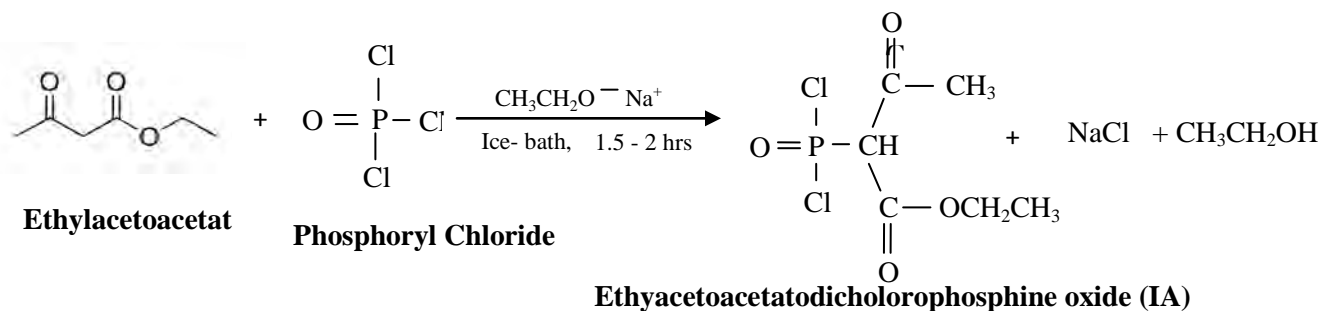
Step 2: The active methylene compounds react with sodium ethoxide to form sodium salt of active methylene compounds at ice-bath.



Step 3: Sodium salt of active methylene compounds then reacts with phosphoryl chloride at ice-bath to form desired compounds.



The over all reactions of different active methylene compounds with phosphoryl chloride to form different phosphine oxide are as follows:



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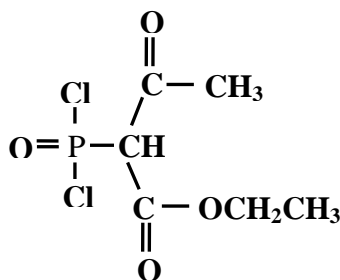
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Chapter 3

RESULTS AND DISCUSSION

3.1 Characterization of Ethylacetoacetato dichloro phosphine oxide



**Ethylacetoacetatodichlorophosphine oxide
(1A)**

The structure of the compound **1A** was established by the spectral evidences such as IR and GC –MS spectral evidences.

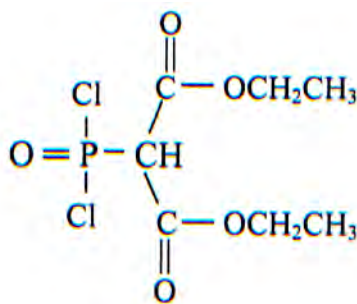
The IR spectrum (**Fig: 1a**) of the compound **1A** showed weak absorption band for aliphatic C-H stretching of the CH₃CO moiety, sharp absorption band at 2923.9 was due to the C-H of OCH₂-CH₃ and another weak band at 2844.8 was designated for C-H stretching of OCH₂-CH₃ moiety.

The wide and intensified band at the range (1720-1620) were assigned for two CO groups of CO-OC₂H₅ and CO-CH₃ and another for P = O group. The P = O group unusually showed absorption band at shorter wavelength due to the attachment of three electronegative atoms with phosphorus atom. The stretching vibrations of two P- Cl bond were observed at 1180 and 1170.7 respectively. The P-C bond vibration was also observed at 1143.7. The other bending vibrations were observed at longer wavelength s not assigned specifically.

The GC-MS (**Fig: 1b**) gave the highest m/z value at 246 which was designated as molecular ion peak.

The spectral evidences support the co-relation with the given structure of the compound **1A**.

3.2 Characterization of Diethylmalonatodichlorophosphine oxide



Diethylmalonatodichlorophosphine oxide
(2A)

The structure of the compound **2A** was identified from the spectral evidences such as IR and GC-MS spectral data.

The IR spectrum (**Fig: 2a**) of the compound **2A** showed moderate absorption band at 2970.2 for C-H stretching of OCH₂-CH₃ moiety. The peak at 2921.9 was also assigned for C-H stretching of another OCH₂-CH₃ moiety. The weak absorption band at 2850.6 was designated for aliphatic C-H stretching of OCH₂-CH₃.

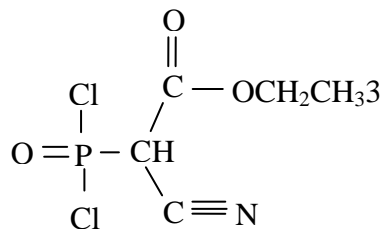
The broad intensified peak at the range (1725-1635.5) were assigned for two CO groups and one P = O group. The two CO groups were indicative for -CO-OC₂H₅ moiety and the other for P = O group relatively at shorter wavelength due to the attachment of three electronegative atoms with P = O group.

The sharp peak at 1450 and 1371 were designated for two P - Cl stretching vibrations. The peak at 1371.13 was assigned for P - C bond vibrations. The other bending vibrations relatively longer wavelengths were not identified specifically.

The GC-MS (**Fig: 2b**) spectral analysis showed the highest molecular ion peak at m/z 264, which expresses co-relation with the structure **2A**.

From the spectral analysis, the structure of the synthesized compound was assigned as **2A**.

3.3 Characterization of Ethylcyanoacetatodichloro phosphine oxide



Ethylcyanoacetatodichlorophosphine oxide (3A)

The structure of the compound **3A** was identified from the spectral evidences such as IR and GC-MS spectral data.

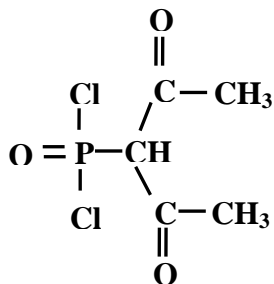
The IR spectrum (**Fig: 3a**) of the compound **3A** showed moderate intensified sharp band at 2997.8 for C – H stretching of – OCH₂ – CH₃ moiety. The aliphatic C – H stretching at 2975 and 2970 were assigned for CH₃ and CH – CN groups respectively. The sharp band at 2237.3 was identified for the triple bond of C≡N. The peak at 1656.7 was designated for carbonyl moiety. It was at relatively lower wavelength due to the labile C-H proton with conjugated with C ≡N.

The P = O group showed sharp band at 1651 relatively at shorter wavelength due to the presence of three electronegative groups attached with phosphorus atom. The two P – Cl bond vibrations were observed at 1446.5 and 1406 respectively. The P-C Stretching frequency was identified at 1384.8. The other bending vibrations were observed at relatively longer wavelength but not specifically designated.

The GC-MS (**Fig: 3b**) showed the highest m/z at 231 as the molecular ion peak, which supports the given structure of the compound **3A**.

The above spectral evidences support the co-relation in favor of the given structure of the compound **3A**.

3.4 Characterization of Acetylacetonatodichlorophosphine oxide



Acetyl acetonatodichlorophosphine oxide
(4A)

The structure of the compound **4A** was confirmed by the spectral evidences such as IR and GC-MS spectral data.

The IR spectrum (**Fig: 4a**) of the compound **4A** showed moderate sharp band at 2921.9 for aliphatic C - H stretching of CH₃CO. The sharp peak at 1633.6 was designated for CO group in conjugation with C-H moiety. The sharp peak at 1600.8 was assigned for P = O group attached with three electronegative groups. The P-Cl stretching frequencies were observed at relatively shorter wavelength. The P - C bond vibration was identified at 1382.9 which is attached with three electropositive groups. The other bending vibrations were not specifically identified.

GC-MS (**Fig: 4b**) spectrum gave the highest m/z at 217 which indicated molecular ion peak of the compound **4A**.

Therefore, the spectral analyses express harmony with the structure of the compound as **4A**.