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Compounds in Organophosphorus Chemistry- Study, Types and Significance

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ABSTRACT: Phosphole is the organic compound with the chemical formula C_4H_4PH ; it is the phosphorus analog of pyrrole. The term phosphole also refers to substituted derivatives of the parent heterocycle. These compounds are of theoretical interest but also serve as ligands for transition metals and as precursors to more complex organophosphorus compounds. Triphosphole, $C_2H_3P_3$, is a heterocycle with 3 phosphorus atoms. Pentaphosphole, P_5H , is a cyclic compound with 5 phosphorus atoms.

KEYWORDS-phosphole, pyrrole, organophosphorus, triphosphole, pentaphosphole

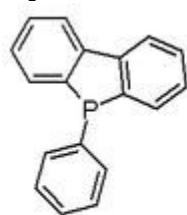
I. INTRODUCTION

Structure and bonding

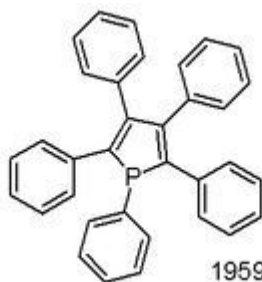
Unlike the related 5-membered heterocycles pyrrole, thiophene, and furan, the aromaticity of phospholes is diminished, reflecting the reluctance of phosphorus to delocalize its lone pair.^[2] The main indication of this difference is the pyramidalization of phosphorus. The absence of aromaticity is also indicated by the reactivity of phospholes.^[3] Phospholes undergo different cycloaddition reactions; coordination properties of phospholes are also well studied.^[4]

Preparation

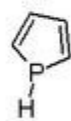
The parent phosphole was first described in 1983. It was prepared by low-temperature protonation of lithium phospholide.^[5] Pentaphenylphosphole was reported in 1953.^[6] One route to phospholes is via the McCormack reaction, involving the addition of a 1,3-diene to a phosphonous chloride ($RPCL_2$) followed [1,2,3] by dehydrohalogenation.^[7] Phenylphospholes can be prepared via zirconacyclopentadienes by reaction with $PhPCl_2$.^[8]



1953



1959



1987

Reactivity

The behavior of the secondary phospholes, those with P-H bond, is dominated by the reactivity of this group.^[5] The parent phosphole readily rearranges by migration of H from P to carbon-2, followed by dimerization.

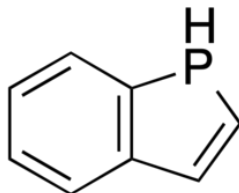
Most phospholes are tertiary, typically P-methyl or P-phenyl. The nonaromaticity of these phospholes is manifested in their reactivity but the P-C bonds remain intact. For example, they undergo Diels-Alder reactions with electrophilic alkynes. They are basic at P, serving as ligands.^[5]

2,5-Diphenyl phospholes can be functionalised by deprotonation followed by P-acylation then a 1H, 2H, 3H phospholide equilibrium resulting in a 1:3 shift of the acyl group.^[9]

Phospholes can also be turned into β -functional phosphabenzenes (phosphinines, or phosphorine) via functionalisation by imidoyl chloride and insertion.^[10]

II.DISCUSSION

Benzophosphole is the organic compound with the chemical formula C_8H_7P ; it is the phosphorus analog of indole.^[2] The term benzophosphole also refers to substituted derivatives of the parent heterocycle.^[4,5,6]



Organophosphorus chemistry is the scientific study of the synthesis and properties of organophosphorus compounds, which are organic compounds containing phosphorus.^[1] They are used primarily in pest control as an alternative to chlorinated hydrocarbons that persist in the environment. Some organophosphorus compounds are highly effective insecticides, although some are extremely toxic to humans, including sarin and VX nerve agents.^[2]

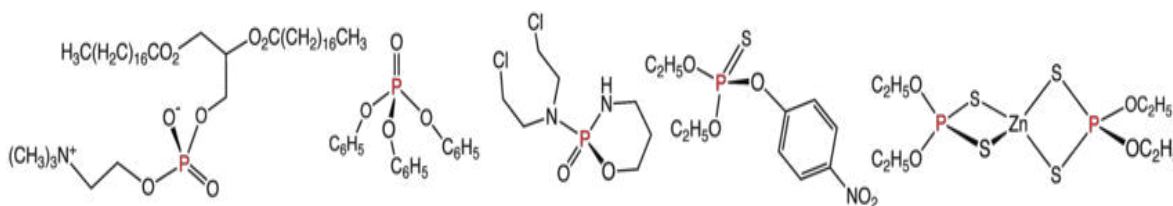
Phosphorus, like nitrogen, is in group 15 of the periodic table, and thus phosphorus compounds and nitrogen compounds have many similar properties.^{[3][4][5]} The definition of organophosphorus compounds is variable, which can lead to confusion. In industrial and environmental chemistry, an organophosphorus compound need contain only an organic substituent, but need not have a direct phosphorus-carbon (P-C) bond.^[citation needed] Thus a large proportion of pesticides (e.g., malathion), are often included in this class of compounds.

Phosphorus can adopt a variety of oxidation states, and it is general to classify organophosphorus compounds based on their being derivatives of phosphorus(V) vs phosphorus(III), which are the predominant classes of compounds. In a descriptive but only intermittently used nomenclature, phosphorus compounds are identified by their coordination number σ and their valency λ . In this system, a phosphine is a $\sigma^3\lambda^3$ compound.^[7,8,9]

A. Organophosphorus(V) compounds, main categories

1) Phosphate esters and amides

Phosphate esters have the general structure $P(=O)(OR)_3$ feature P(V). Such species are of technological importance as flame retardant agents, and plasticizers. Lacking a P-C bond, these compounds are in the technical sense not organophosphorus compounds but esters of phosphoric acid. Many derivatives are found in nature, such as phosphatidylcholine. Phosphate ester are synthesized by alcoholysis of phosphorus oxychloride. A variety of mixed amido-alkoxo derivatives are known, one medically significant example being the anti-cancer drug cyclophosphamide. Also derivatives containing the thiophosphoryl group (P=S) include the pesticide malathion. The organophosphates prepared on the largest scale are the zinc dithiophosphates, as additives for motor oil. Several million kilograms of this coordination complex are produced annually by the reaction of phosphorus pentasulfide with alcohols.^[6]



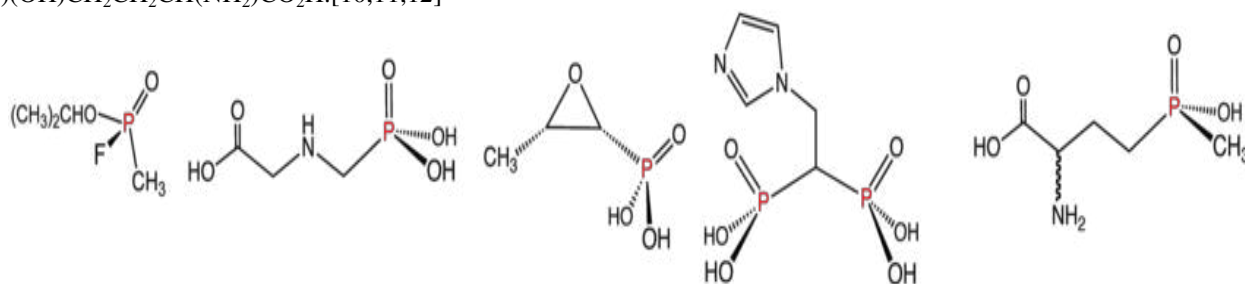
Illustrative organophosphates and related compounds: phosphatidylcholine, triphenylphosphate, cyclophosphamide, parathion, and zinc dithiophosphate.

In the environment, these compounds break down via hydrolysis to eventually afford phosphate and the organic alcohol or amine from which they are derived.

2) *Phosphonic and phosphinic acids and their esters*

Phosphonates are esters of phosphonic acid and have the general formula $RP(=O)(OR')_2$. Phosphonates have many technical applications, a well-known member being glyphosate, better known as Roundup. With the formula $(HO)_2P(O)CH_2NHCH_2CO_2H$, this derivative of glycine is one of the most widely used herbicides. Bisphosphonates are a class of drugs to treat osteoporosis. The nerve gas agent sarin, containing both C–P and F–P bonds, is a phosphonate.

Phosphinates feature two P–C bonds, with the general formula $R_2P(=O)(OR')$. A commercially significant member is the herbicide glufosinate. Similar to glyphosate mentioned above, it has the structure $CH_3P(O)(OH)CH_2CH_2CH(NH_2)CO_2H$. [10,11,12]



Illustrative examples of phosphonates and phosphinates in the order shown: Sarin (phosphonate), Glyphosate (phosphonate), fosfomycin (phosphonate), zoledronic acid (phosphonate), and Glufosinate (phosphinate). In aqueous solution, phosphonic acids ionize to give the corresponding organophosphonates.

The Michaelis–Arbuzov reaction is the main method for the synthesis of these compounds. For example, dimethylmethylphosphonate (see figure above) arises from the rearrangement of trimethylphosphite, which is catalyzed by methyl iodide. In the Horner–Wadsworth–Emmons reaction and the Seyferth–Gilbert homologation, phosphonates are used in reactions with carbonyl compounds. The Kabachnik–Fields reaction is a method for the preparation of aminophosphonates. These compounds contain a very inert bond between phosphorus and carbon. Consequently, they hydrolyze to give phosphonic and phosphinic acid derivatives, but not phosphite.

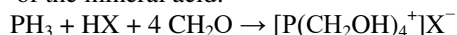
3) *Phosphine oxides, imides, and chalcogenides [13,14]*

Phosphine oxides (designation $\sigma^4\lambda^5$) have the general structure $R_3P=O$ with formal oxidation state V. Phosphine oxides form hydrogen bonds and some are therefore soluble in water. The P=O bond is very polar with a dipole moment of 4.51 D for triphenylphosphine oxide.

Compounds related to phosphine oxides include phosphine imides (R_3PNR') and related chalcogenides (R_3PE , where E = S, Se, Te). These compounds are some of the most thermally stable organophosphorus compounds.

4) *Phosphonium salts and phosphoranes*

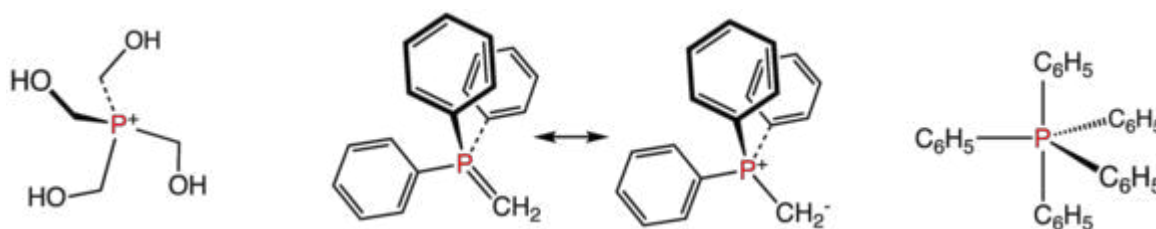
Compounds with the formula $[PR_4^+]X^-$ comprise the phosphonium salts. These species are tetrahedral phosphorus(V) compounds. From the commercial perspective, the most important member is tetrakis(hydroxymethyl)phosphonium chloride, $[P(CH_2OH)_4]Cl$, which is used as a fire retardant in textiles. Approximately 2M kg are produced annually of the chloride and the related sulfate.^[6] They are generated by the reaction of phosphine with formaldehyde in the presence of the mineral acid:



A variety of phosphonium salts can be prepared by alkylation and arylation of organophosphines:

$$PR_3 + R'X \rightarrow [PR_3R'^+]X^-$$

The methylation of triphenylphosphine is the first step in the preparation of the Wittig reagent.



Illustrative phosphorus(V) compounds: the phosphonium ion $\text{P}(\text{CH}_2\text{OH})_4^+$, two resonance structures for the Wittig reagent Ph_3PCH_2 , and pentaphenylphosphorane, a rare pentaorganophosphorus compound.

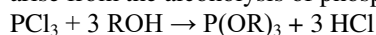
The parent phosphorane ($\sigma^5\lambda^5$) is PH_5 , which is unknown.^[citation needed] Related compounds containing both halide and organic substituents on phosphorus are fairly common. Those with five organic substituents are rare, although $\text{P}(\text{C}_6\text{H}_5)_5$ is known, being derived from $\text{P}(\text{C}_6\text{H}_5)_4^+$ by reaction with phenyllithium.[15,16,17]

Phosphorus ylides are unsaturated phosphoranes, known as Wittig reagents, e.g. $\text{CH}_2\text{P}(\text{C}_6\text{H}_5)_3$. These compounds feature tetrahedral phosphorus(V) and are considered relatives of phosphine oxides. They also are derived from phosphonium salts, but by deprotonation not alkylation.

B. Organophosphorus(III) compounds, main categories

1) Phosphites, phosphonites, and phosphinites

Phosphites, sometimes called phosphite esters, have the general structure $\text{P}(\text{OR})_3$ with oxidation state +3. Such species arise from the alcoholysis of phosphorus trichloride:



The reaction is general, thus a vast number of such species are known. Phosphites are employed in the Perkow reaction and the Michaelis–Arbuzov reaction. They also serve as ligands in organometallic chemistry.

Intermediate between phosphites and phosphines are phosphonites ($\text{P}(\text{OR})_2\text{R}'$) and phosphinite ($\text{P}(\text{OR})\text{R}'_2$). Such species arise via alcoholysis reactions of the corresponding phosphonous and phosphinous chlorides ($(\text{PCl}_2\text{R}')$ and (PClR'_2) , respectively).

2) Phosphines

The parent compound of the phosphines is PH_3 , called phosphine in the US and British Commonwealth, but phosphane elsewhere.^[7] Replacement of one or more hydrogen centers by an organic substituents (alkyl, aryl), gives $\text{PH}_{3-x}\text{R}_x$, an organophosphine, generally referred to as phosphines.

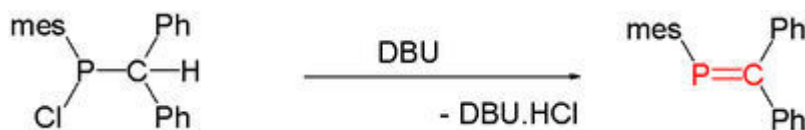
From the commercial perspective, the most important phosphine is triphenylphosphine, several million kilograms being produced annually. It is prepared from the reaction of chlorobenzene, PCl_3 , and sodium.^[6] Phosphines of a more specialized nature are usually prepared by other routes.^[8] Phosphorus halides undergo nucleophilic displacement by organometallic reagents such as Grignard reagents. Organophosphines are nucleophiles and ligands. Two major applications are as reagents in the Wittig reaction and as supporting phosphine ligands in homogeneous catalysis.[18]

Their nucleophilicity is evidenced by their reactions with alkyl halides to give phosphonium salts. Phosphines are nucleophilic catalysts in organic synthesis, e.g. the Rauhut–Currier reaction and Baylis–Hillman reaction. Phosphines are reducing agents, as illustrated in the Staudinger reduction for the conversion of organic azides to amines and in the Mitsunobu reaction for converting alcohols into esters. In these processes, the phosphine is oxidized to phosphorus(V). Phosphines have also been found to reduce activated carbonyl groups, for instance the reduction of an α -keto ester to an α -hydroxy ester.^[9]

3) Phosphaalkenes and phosphaalkynes

Compounds with carbon phosphorus(III) multiple bonds are called phosphaalkenes ($\text{R}_2\text{C}=\text{PR}$) and phosphaalkynes ($\text{RC}\equiv\text{P}$). They are similar in structure, but not in reactivity, to imines ($\text{R}_2\text{C}=\text{NR}$) and nitriles ($\text{RC}\equiv\text{N}$), respectively. In the compound phosphorine, one carbon atom in benzene is replaced by phosphorus. Species of this type are relatively rare but for that reason are of interest to researchers. A general method for the synthesis

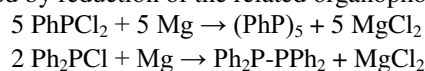
of phosphalkenes is by 1,2-elimination of suitable precursors, initiated thermally or by base such as DBU, DABCO, or triethylamine:



Thermolysis of Me_2PH generates $\text{CH}_2=\text{PMe}$, an unstable species in the condensed phase.

C. Organophosphorus(0), (I), and (II) compounds

Compounds where phosphorus exists in a formal oxidation state of less than III are uncommon, but examples are known for each class. Organophosphorus(0) species are debatably illustrated by the carbene adducts, $[\text{P}(\text{NHC})]_2$, where NHC is an N-heterocyclic carbene.^[10] With the formulae $(\text{RP})_n$ and $(\text{R}_2\text{P})_2$, respectively, compounds of phosphorus(I) and (II) are generated by reduction of the related organophosphorus(III) chlorides:



Diphosphenes, with the formula R_2P_2 , formally contain phosphorus-phosphorus double bonds. These phosphorus(I) species are rare but are stable provided that the organic substituents are large enough to prevent catenation. Many mixed-valence compounds are known, e.g. the cage $\text{P}_7(\text{CH}_3)_3$.

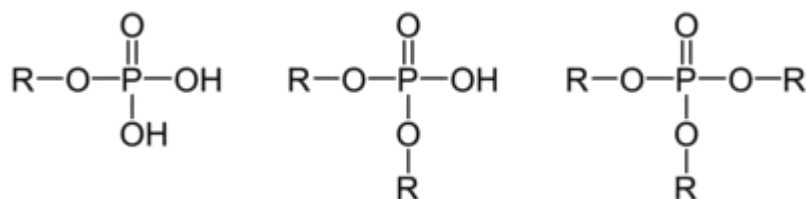
III.RESULTS

In organic chemistry, organophosphates (also known as phosphate esters, or OPEs) are a class of organophosphorus compounds with the general structure $\text{O}=\text{P}(\text{OR})_3$, a central phosphate molecule with alkyl or aromatic substituents.^[1] They can be considered as esters of phosphoric acid.

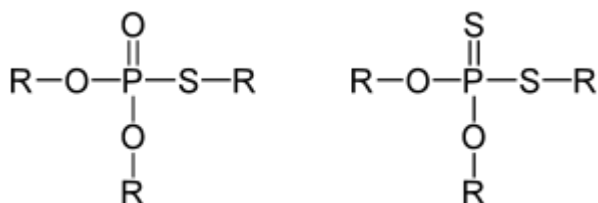
Like most functional groups, organophosphates occur in a diverse range of forms,^[2] with important examples including key biomolecules such as DNA, RNA and ATP, as well as many insecticides, herbicides, nerve agents and flame retardants. OPEs have been widely used in various products as flame retardants, plasticizers, and performance additives to engine oil. The popularity of OPEs as flame retardants came as a substitution for the highly regulated brominated flame retardants.^[3] The low cost of production and compatibility to diverse polymers made OPEs to be widely used in industry including textile, furniture, electronics as plasticizers and flame retardants. These compounds are added to the final product physically rather than by chemical bond.^[4] Due to this, OPEs leak into the environment more readily through volatilization, leaching, and abrasion.^[5] OPEs have been detected in diverse environmental compartments such as air, dust, water, sediment, soil and biota samples at higher frequency and concentration.^{[1][5]}

D. Forms

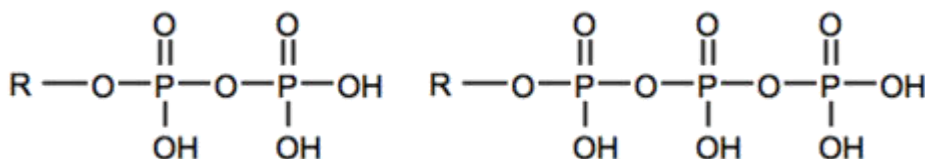
Organophosphates are a class of compounds encompassing a number of distinct but closely related function groups. These are primarily the esters of phosphoric acid and can be mono-esters, di-esters or tri-esters depending on the number of attached organic groups (abbreviated as 'R' in the image below). In general man-made organophosphates are most often triesters, while biological organophosphates are usually mono- or di-esters. The hydrolysis of triesters can form diesters and monoesters.^[6]



In the context of pesticides, derivatives of organophosphates such as organothiophosphates ($\text{P}=\text{S}$) or phosphorodiamidates ($\text{P}-\text{N}$) are included as being organophosphates. The reason is that these compound are converted into organophosphates biologically.[17,18,19]



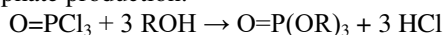
In biology the esters of diphosphoric acid and triphosphoric acid are generally included as organophosphates. The reason is again a practical one, as many cellular processes involve the mono- di and tri- phosphates of the same compound. For instance, the phosphates of adenosine (AMP, ADP, ATP) play a key role in many metabolic processes.



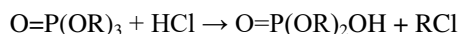
E. Synthesis

Alcoholysis of POCl_3

Phosphorus oxychloride reacts readily with alcohols to give organophosphates. This is the dominate industrial route and is responsible for almost all organophosphate production.



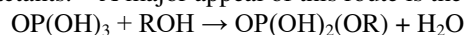
When aliphatic alcohols are used the HCl by-product can react with the phosphate esters to give organochlorides and a lower ester.



This reaction is usually undesirable and is exacerbated by high reaction temperatures. It can be inhibited by the use of a base or the removal of HCl through sparging.

Esterification of phosphoric acid and P_2O_5

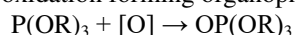
Esterifications of phosphoric acid with alcohols proceed less readily than the more common carboxylic acid esterifications, with the reactions rarely proceeding much further than the phosphate mono-ester. The reaction requires high temperatures, under which the phosphoric acid can dehydrate to form poly-phosphoric acids. These are exceedingly viscous and their linear polymeric structure renders them less reactive than phosphoric acid.^[7] Despite these limitations the reaction does see industrial use for the formation of monoalkyl phosphates, which are used as surfactants.^[8] A major appeal of this route is the low cost of phosphoric acid compared to phosphorus oxychloride.



P_2O_5 is the anhydride of phosphoric acid and acts similarly. The reaction yields equimolar amounts of di- and monoesters with no phosphoric acid. The process is mostly limited to primary alcohols, as secondary alcohols are prone to undesirable side reactions such as dehydration.^[9]

Oxidation of phosphite esters

Organophosphites can be easily oxidised to give organophosphates. This might ordinarily be considered a specialised method, however large quantities of organophosphites are produced as antioxidant stabilisers for plastics, with their gradual oxidation forming organophosphates in the human environment.^{[10][11]}



Phosphorylation

The formation of organophosphates is an important part of biochemistry and living systems achieve this using a variety of enzymes. Phosphorylation is essential to the processes of both anaerobic and aerobic respiration, which involve the production of adenosine triphosphate (ATP), the "high-energy" exchange medium in the cell.

*F. Properties*1) *Bonding*

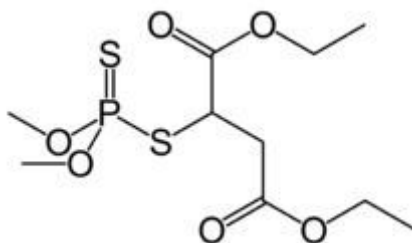
The bonding in organophosphates has been a matter of prolonged debate; the phosphorus atom is classically hypervalent, as it possesses more bonds than the octet rule should allow.^[12] The focus of debate is usually on the nature of the phosphoryl P=O bond, which displays (in spite of the common depiction) non-classical bonding, with a bond order somewhere between 1 and 2. Early papers explained the hypervalence in terms of d-orbital hybridisation, with the energy penalty of promoting electrons into the higher energy orbitals being off-set by the stabilisation of additional bonding.^[13] Later advances in computational chemistry showed that d-orbitals played little significant role in bonding.^{[14][15]} Current models rely on either negative hyperconjugation,^[16] or a more complex arrangement with a dative-type bond from P to O, combined with back-donation from a 2p orbital on the oxygen.^{[15][17]} These models agree with the experimental observations of the phosphoryl as being shorter than P-OR bonds^[18] and much more polarised. It has been argued that a more accurate depiction is dipolar (i.e. $(RO)_3P^+O^-$),^[19] which is similar to the depiction phosphorous ylides such as methylenetriphenylphosphorane. However in contrast to ylides, the phosphoryl group is unreactive and organophosphates are poor nucleophiles, despite the high concentration of charge on the phosphoryl oxygen. The polarisation accounts in part for the higher melting points of phosphates when compared to their corresponding phosphites. The bonding in penta-coordinate phosphoranes (i.e. $P(OR)_5$) is entirely different and involves three-center four-electron bonds.

2) *Acidity*

Phosphate esters bearing P-OH groups are acidic. The pKa of the first OH group is typically between 1-2, with the second OH deprotonating at a pKa of 6-7.^[20] This is of great practical importance as it means that phosphate mono- and di-esters are negatively charged at physiological pH (due to deprotonation).^[21] This includes biomolecules such as DNA and RNA. The presence of this negative charge makes these compounds much more water soluble, and also more resistant to degradation by hydrolysis or other forms of nucleophilic attack.^[22]

3) *Water solubility*

The water solubility of organophosphates is an important factor in biological, industrial and environmental settings. The wide variety of substitutes used in organophosphate esters results in great variations in physical properties. OPEs exhibit a wide range of octanol/water partition coefficients where log Kow values range from -0.98 up to 10.6.^[3] Mono- and di-esters are usually water soluble, particularly biomolecules. Tri-esters such as flame retardants and plasticisers have positive log Kow values ranging between 1.44 and 9.49, signifying hydrophobicity.^{[3][23][5][24]} Hydrophobic OPEs are more likely to be bioaccumulated and biomagnified in aquatic ecosystems.^[4] Halogenated organophosphates tend to be denser than water and sink, causing them to accumulate in sediments.^[25]

*G. Industrial materials*1) *Pesticides*

Malathion, one of the first organophosphate insecticides. It remains important as a Vector control agent.

Organophosphates are best known for their use as pesticides. The vast majority are insecticides and are used either to protect crops, or as vector control agents to reduce the transmission of diseases spread by insects, such as mosquitoes. Health concerns have seen their use significantly decrease since the turn of the century.^{[26][27]} Glyphosate is sometimes called an organophosphate, but is in-fact a phosphonate. Its chemistry, mechanism of toxicity and end-use as a herbicide are different from the organophosphate insecticides.

The development of organophosphate insecticides dates back to the 1930s and is generally credited to Gerhard Schrader.^[28] At the time pesticides were largely limited to arsenic salts (calcium arsenate, lead arsenate and Paris

green)^[29] or pyrethrin plant extracts, all of which had major problems.^[30] Schrader was seeking more effective agents, however while some organophosphates were found to be far more dangerous to insects than higher animals,^[31] the potential effectiveness of others as chemical weapons did not go unnoticed. The development of organophosphate insecticides and the earliest nerve agents was conjoined, with Schrader also developing the nerve agents tabun and sarin. Organophosphate pesticides were not commercialised until after WWII. Parathion was among the first marketed, followed by malathion and azinphosmethyl. Although organophosphates were used in considerable quantities they were originally less important than organochlorine insecticides such as DDT, dieldrin, and heptachlor.

Organophosphate insecticides are acetylcholinesterase inhibitors, and when introduced to an organism they act to fatally disrupt the transmission of nerve signals. The risk of human death through organophosphate poisoning^[32] was obvious from the start and led to efforts to lower toxicity against mammals while not reducing efficacy against insects.^{[33][34]}

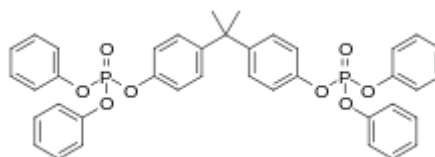
The majority of organophosphate insecticides are organothiophosphates (P=S) or phosphorodiamidates (P-N), both of which are significantly weaker acetylcholinesterase inhibitors than the corresponding phosphates (P=O). They are 'activated' biologically by the exposed organism, via oxidative conversion of P=S to P=O,^[35] hydroxylation,^{[36][37]} or other related process which see them transformed into organophosphates. In mammals these transformations occur almost exclusively in the liver,^[38] while in insects they take place in the gut and fat body.^{[39][40][41]} As the transformations are handled by different enzymes in different classes of organism it is possible to find compounds which activate more rapidly and completely in insects, and thus display more targeted lethal action.

This selectivity is far from perfect and organophosphate insecticides remain acutely toxic to humans, with many thousands estimated to be killed each year due to intentional (suicide)^[42] or unintentional poisoning. Beyond their acute toxicity, exposure to organophosphates is associated with a number of health risks, including organophosphate-induced delayed neuropathy (muscle weakness) and developmental neurotoxicity.^{[28][43][44]} There is limited evidence that certain compounds cause cancer, including malathion and diazinon.^[45] Children^[46] and farmworkers^[47] are considered to be at greater risk.

Pesticide regulation in the United States and the regulation of pesticides in the European Union have both been increasing restrictions on organophosphate pesticides since the 1990s, particularly when used for crop protection. The use of organophosphates has decreased considerably since that time, having been replaced by pyrethroids and neonicotinoids, which are effective at a much lower levels.^[48] Reported cases of organophosphate poisoning in the US have reduced during this period.^{[49][50]} Regulation in the global south can be less extensive.^{[51][52]}

In 2015, only 3 of the 50 most common crop-specific pesticides used in the US were organophosphates (Chlorpyrifos, Bensulide, Acephate),^[53] of these Chlorpyrifos was banned in 2021.^[54] No new organophosphate pesticides have been commercialised in the 21st century.^[55] The situation in vector control is fairly similar, despite different risk trade-offs,^[56] with the global use of organophosphate insecticides falling by nearly half between 2010 and 2019.^[27] Pirimiphos-methyl, Malathion and Temefos are still important, primarily for the control of malaria in the Asia-Pacific region.^[27] The continued use of these agents is being challenged by the emergence of insecticide resistance.^[57]

2)

Flame retardants

Bisphenol A diphenyl phosphate, a common organophosphate flame retardant

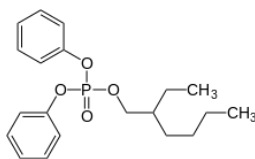
Flame retardants are added to materials to prevent combustion and to delay the spread of fire after ignition. Organophosphate flame retardants are part of a wider family of phosphorous-based agents which include organic phosphonate and phosphinate esters, in addition to inorganic salts.^{[58][59]} When some prominent brominated flame retardant were banned in the early 2000s phosphorous-based agents were promoted as safer replacements. This has led to a large increase in their use, with an estimated 1 million tonnes of organophosphate flame retardants produced in 2018.^[60] Safety concerns have subsequently been raised about some of these reagents,^{[61][62]} with several under regulatory scrutiny.^{[63][64]}

Organophosphate flame retardants were first developed in the first half of the twentieth century in the form of triphenyl phosphate, tricresyl phosphate and tributyl phosphate for use in plastics like cellulose nitrate and cellulose acetate.^[65] Use in cellulose products is still significant, but the largest area of application is now in plasticized vinyl polymers, principally PVC. The more modern organophosphate flame retardants come in 2 major types; chlorinated aliphatic compounds or aromatic diphosphates.^[58] The chlorinated compounds TDCPP, TCPP and TCEP are all involatile liquids, of which TCPP is perhaps the most important. They are used in polyurethane (insulation, soft furnishings), PVC (wire and cable) phenolic resins and epoxy resins (varnishes, coatings and adhesives). The most important of the diphosphates is bisphenol-A bis(diphenyl phosphate), with related analogues based around resorcinol and hydroquinone. These are used in polymer blends of engineering plastics, such as PPO/HIPS and PC/ABS,^[66] which are commonly used to make casing for electrical items like TVs, computers and home appliances.

Organophosphates act multifunctionally to retard fire in both the gas phase and condensed (solid) phase. Halogenated organophosphates are more active overall as their degradation products interfere with combustion directly in the gas phase. All organophosphates have activity in the condensed phase, by forming phosphorus acids which promote char formation, insulating the surface from heat and air.

Organophosphates were originally thought to be a safe replacements for brominated flame retardants, however many are now coming under regulatory pressure due to their apparent health risks.^{[64][67][68]} The chlorinated organophosphates may be carcinogenic, while others such as tricresyl phosphate have necrotic properties.^[69] Bisphenol-A bis(diphenyl phosphate) can hydrolyse to form Bisphenol-A which is under significant scrutiny as potential endocrine-disrupting chemical. Although their names imply that they are a single chemical, many are actually produced as complex mixtures. For instance, commercial grade TCPP can contain 7 different isomers,^[70] while tricresyl phosphate can contain up to 10.^[71] This makes their safety profiles harder to ascertain, as material from different producers can have different compositions.^[72]

3)

Plasticisers

2-Ethylhexyl diphenyl phosphate an alkyl diaryl organophosphate used as both a plasticizer and flame retardant in PVC

Plasticisers are added to polymers and plastics to improve their flexibility and processability, giving a softer more easily deformable material. In this way brittle polymers can be made more durable. Organophosphates find use because they are multifunctional; primarily plasticising but also imparting flame resistance. The most frequently plasticised polymers are the vinyls (PVC, PVB, PVA and PVCA), as well as cellulose plastics (cellulose acetate, nitrocellulose and cellulose acetate butyrate).^[73] PVC dominates the market, consuming 80-90% of global plasticiser production.^{[73][74]} PVC can accept large amounts of plasticiser; a PVC item may be 70-80% plasticiser by mass in extreme cases, but loadings of between 0-50% are more common.^[75] The main applications of these products are in wire and cable insulation, flexible pipe, automotive interiors, plastic sheeting, vinyl flooring, and toys.

Pure PVC is more than 60% chlorine by mass and difficult to burn, but its flammability increases the more it is plasticised.^[76] Organophosphates can act as both plasticisers and flame retarders. Compounds used are typically triaryl or alkyl diaryl phosphates, with cresyl diphenyl phosphate and 2-ethylhexyl diphenyl phosphate being important respective example.^[77] These are both liquids with high boiling points. Organophosphates are more expensive than traditional plasticisers and so tend to be used in combination with other plasticisers and flame retardants.^[78]

4)

Hydraulic fluids and lubricant additives

Similar to their use as plasticisers, organophosphates are well suited to use as hydraulic fluids due to their low freezing points and high boiling points, fire-resistance, non-corrosiveness, excellent boundary lubrication properties and good general chemical stability. The triaryl phosphates are the most important group, with tricresyl phosphate being the first to be commercialised in the 1940s, with trixylyl phosphate following shortly after. Butylphenyl diphenyl phosphate and propylphenyl diphenyl phosphate became available after 1960.^[79]

In addition to their use as hydraulic base-stock, organophosphates (tricresyl phosphate) and metal organothiophosphates (zinc dithiophosphate) are used as both an antiwear additives and extreme pressure additives in lubricants, where they remain effective even at high temperatures.^{[80][81][82]}

5) *Metal extractants*

Organophosphates have long been used in the field of extractive metallurgy to liberate valuable rare earths from their ores.^[83] Di(2-ethylhexyl)phosphoric acid and tributyl phosphate are used for the liquid-liquid extraction of these elements from the acidic mixtures form by the leaching of mineral deposits.^[84] These compounds are also used for the PUREX (plutonium uranium reduction extraction) process, which is used for nuclear reprocessing.^[85]

6) *Surfactants*

Mono- and di-phosphate esters of alcohols or alcohol ethoxylates are used as surfactants (detergents).^[86] Compared to the more common sulfur-based anionic surfactants (such as LAS or SLES), phosphate ester surfactants are more expensive and generate less foam.^[86] Benefits include stability over a broad pH range, low skin irritation and a high tolerance to dissolved salts.^[87] In agricultural settings monoesters of fatty alcohol ethoxylates are used, which are able to disperse poorly miscible or insoluble pesticides into water. As they are low-foaming these mixtures can be sprayed effectively onto fields, while a high salt tolerance allows co-spraying of pesticides and inorganic fertilisers.^[88] Low-levels of phosphate mono-esters, such as potassium cetyl phosphate, find use in cosmetic creams and lotions.^[89] These in oil-in-water formulations are primarily based on non-ionic surfactants, with the anionic phosphate acting as emulsion-stabilisers. Phosphate tri-esters such as tributyl phosphate are used as anti-foaming agent in paints and concrete.

7) *Nerve agents*

Although the first phosphorous compounds observed to act as cholinesterase inhibitors were organophosphates,^[90] the vast majority of nerve agents are instead phosphonates containing a P-C bond. Only a handful of organophosphate nerve agents were developed between the 1930s and 1960s, including diisopropylfluorophosphate, VG and NPF. Between 1971 and 1993 the Soviet Union developed many new potential nerve agents, commonly known as the Novichok agents.^[91] Some of these can be considered organophosphates (in a broad sense), being derivatives of fluorophosphoric acid. Examples include A-232, A-234, A-262, C01-A035 and C01-A039. The most notable of these is A-234, which was claimed to be responsible for the poisoning of Sergei and Yulia Skripal in Salisbury (UK) 2018.^[92]

H. In nature

The detection of OPEs in the air as far away as Antarctica at concentrations around 1 ng/m³ suggests their persistence in air, and their potential for long-range transport.^[24] OPEs were measured in high frequency in air and water and widely distributed in northern hemisphere.^{[93][94]} The chlorinated OPEs (TCEP, TCIPP, TDCIPP) in urban sampling sites and non-halogenated like TBOEP in rural areas respectively were frequently measured in the environment across multiple sites. In the Laurentian Great Lakes total OPEs concentrations were found to be 2–3 orders of magnitude higher than concentrations of brominated flame retardants measured in similar air.^[94] Waters from rivers in Germany, Austria, and Spain have been consistently recorded for TBOEP and TCIPP at highest concentrations.^[24] From these studies, it is clear that OPE concentrations in both air and water samples are often orders of magnitude higher than other flame retardants, and that concentrations are largely dependent on sampling location, with higher concentrations in more urban, polluted locations.

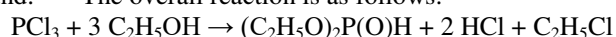
IV. CONCLUSION

In organic chemistry, a phosphite ester or organophosphite usually refers to an organophosphorous compound with the formula P(OR)₃. They can be considered as esters of an unobserved tautomer phosphorous acid, H₃PO₃, with the simplest example being trimethylphosphite, P(OCH₃)₃. Some phosphites can be considered esters of the dominant tautomer of phosphorous acid (HP(O)(OH)₂). The simplest representative is dimethylphosphite with the formula HP(O)(OCH₃)₂. Both classes of phosphites are usually colorless liquids.

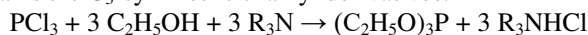
I. Synthesis

From PCl₃

Phosphite esters are typically prepared by treating phosphorus trichloride with an alcohol. For alkyl alcohols the displaced chloride ion can attack the phosphite, causing dealkylation to give a dialkylphosphite and an organochlorine compound.^{[1][2]} The overall reaction is as follows:



Alternatively, when the alcoholysis is conducted in the presence of proton acceptors (typically an amine base), one obtains the C₃-symmetric trialkyl derivatives:^[3]



A base is not essential when using aromatic alcohols such as phenols, as they are not susceptible to attack by chloride, however it does catalyse the esterification reaction and is therefore often included.^[4]

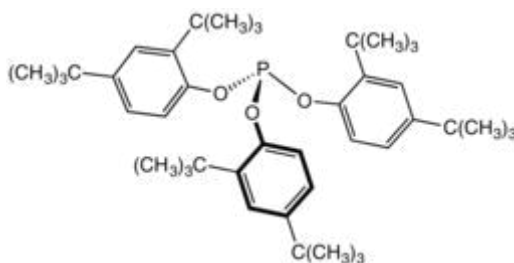
By transesterification

Phosphite esters can also be prepared by transesterification, as they undergo alcohol exchange upon heating with other alcohols.^[5] This process is reversible and can be used to produce mixed alkyl phosphites. Alternatively, if the phosphite of a volatile alcohol is used, such as trimethyl phosphite, then the by product (methanol) can be removed by distillation, allowing the reaction to be driven to completion.

J. Reactions and applications of tris(organo)phosphites

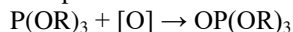
1)

Reactions



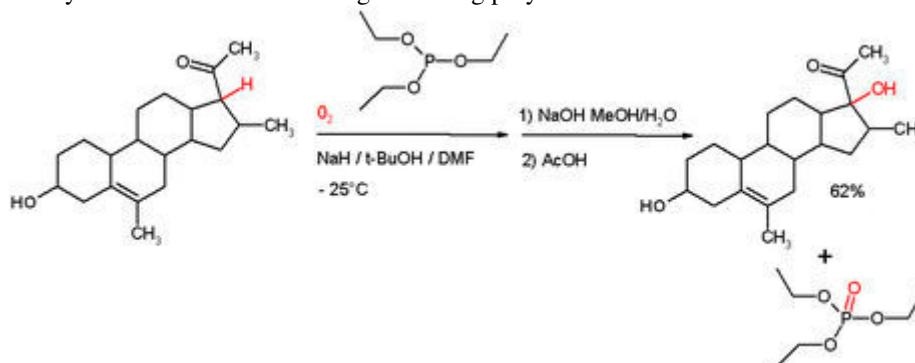
Tris(2,4-di-tert-butylphenyl)phosphite, a widely used stabilizer in polymers[20,21]

Phosphites are oxidized to phosphate esters:



This reaction underpins the commercial use of some phosphite esters as stabilizers in polymers.^[6]

Alkyl phosphite esters are used in the Perkow reaction for the formation of vinyl phosphonates, and in the Michaelis–Arbuzov reaction to form phosphonates. Aryl phosphite esters may not undergo these reactions and hence are commonly used as stabilizers in halogen-bearing polymers such as PVC.



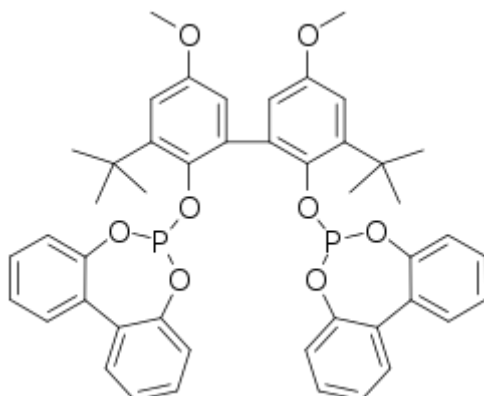
Autoxidation of a keto steroid with oxygen to the hydroperoxide (not depicted) followed by reduction with triethylphosphite to the alcohol

Phosphite esters may be used as reducing agents in more specialised cases. For example, triethylphosphite is known to reduce certain hydroperoxides to alcohols formed by autoxidation^[7] (scheme). In this process the phosphite is converted to a phosphate ester. This reaction type is also utilized in the Wender Taxol total synthesis.^[8]

2)

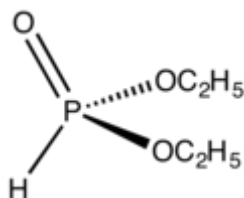
Homogeneous catalysis

Phosphite esters are Lewis bases and hence can form coordination complexes with various metal ions. Representative phosphite ligands include trimethylphosphite ((MeO)₃P), triethylphosphite ((EtO)₃P), trimethylolpropane phosphite, and triphenylphosphite ((PhO)₃P). Phosphites exhibit a smaller ligand cone angles than the structurally related phosphine ligand family. Phosphite ligands are components of industrial catalysts for hydroformylation and hydrocyanation.^[8]



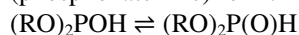
BiPhePhos is representative diphosphite ligand used in homogeneous catalysis.^{[9][10]}

K. Chemistry of $HP(O)(OR)_2$



Structure of a diethylphosphite.

Diorganophosphites are derivatives of phosphorus(V) and can be viewed as the di-esters of phosphorous acid $((HO)_2P(O)H)$. They exhibit tautomerism, however, the equilibrium overwhelmingly favours the right-hand (phosphonate-like) form:^{[11][12]}



The P-H bond is the site of high reactivity in these compounds (for example in the Atherton–Todd reaction and Hirao coupling), whereas in tri-organophosphites the lone pair on phosphorus is the site of high reactivity. Diorganophosphites do however undergo transesterification.^[22]

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