Organophosphorus Pesticides: Organic and Biological Chemistry

Author:

Morifusa Eto

Organophosphorus Pesticides: Organic and Biological Chemistry

Author:

Morifusa Eto

Department of Agricultural Chemistry
Kyushu University
Fukuoka, Japan

PREFACE

Recent development in the pure and applied chemistry of organophosphorus compounds is amazing. Even though the organic derivatives of phosphoric acid occupy only a part of the family of organophosphorus compounds, the variation of the four groups attached to the phosphorus atom is almost infinite, and they display a great variety of significant biological activities. Many partial esters play essential roles in normal biological systems, whereas many neutral derivatives display biocidal activities. Since the finding of insecticidal activity in the latter part of the 1930's by Schrader, a number of neutral phosphate derivatives have been developed into practical insecticides. Owing to their high activity and biodegradability, their application to agriculture, public health, and related fields has been growing rapidly. Moreover, the pesticidal activities of organophosphorus compounds, which are not restricted to phosphate derivatives, also include acaricidal, nematocidal, anthelmintic, insect sterilizing, fungicidal, herbicidal, and rodenticidal activities.

In order to get a general concept of organophosphorus pesticides with such a variety in structure and biological activities, consideration of each aspect of chemistry, biochemistry, and the applied sciences is necessary. This book consists of these three main parts. After the presentation of the background of phosphorus chemistry in Chapter I, stress was put on the chemical and biochemical reactions of organophosphorus pesticides, including synthesis, analysis, metabolism mode of action, and other interesting aspects in Chapters II to IV, and on the structure-pesticidal activity relationship in Chapter V. Almost all commercialized and important experimental organophosphorus pesticides are mentioned. Unlike insecticides, the mode of action of other pesticides is not well established, and the scattered knowledge about them is difficult to generalize. They are described in the corresponding sections of Chapter V, "Individual Pesticides." Although this book is designed as a readable text, it has reference value also. It is the author's pleasure that this book will not only be useful to students and beginners, but will also assist specialists dealing with pesticides.

TABLE OF CONTENTS

Chapter III
Chemical Reactions

Chapter IV
Biochemistry

Chapter I

INTRODUCTION

A. HISTORY

Organic compounds of phosphorus are the essential constituent of protoplasm and play important roles for maintenance of life, for example, as nucleic acids, nucleotide coenzymes, metabolic intermediates, and phosphatides. On the other hand, many organophosphorus compounds are artificially produced for the practical uses of lubricants, oil additives, plasticizers, and pesticides.[1] Organophosphorus pesticides include not only insecticides, but also fungicides, herbicides, and others. It is surprising to know that such great varieties in chemical, physical, and biological properties are governed by the selection of groups attached on the phosphorus atom.

The research in the field of the organic chemistry of phosphorus was first undertaken by Lassaigne, in 1820, to prepare phosphate esters.[2] The chemistry of organophosphorus compounds was developed extensively by Michaelis in Germany, during the late 19th century and the beginning of this century.[3] He performed many works and gave a foundation for this field, particularly on the chemistry of compounds containing the P-N bond.[4] Overlapping the latter stages of Michaelis, a Russian chemist, A. E. Arbuzov, conducted extensive research, especially on the chemistry of trivalent phosphorus compounds, including the famous Michaelis-Arbuzov reaction to form the P-C linkage.[5] His work has been continued by his son, B. A. Arbuzov.

On the other hand, since Harden and Young disclosed, in 1905, the importance of inorganic phosphate on alcoholic fermentation and discovered fructose diphosphate as a metabolic intermediate,[6] many interesting organic phosphate esters have been found from biological sources. Since 1945, a systematic investigation on phosphorylation reactions has been carried out by the school of Sir Todd, and then by Cramer, in order to synthesize naturally occurring phosphate esters.[7,8]

Physiologically abnormal effects of organophosphorus compounds were first observed in dialkyl phosphorofluoridates by Lange and Krueger in 1932.[9] They intended to find new types of organic pesticides at that time.[10] During the Second War, Saunders in England and Schrader in Germany worked on toxic phosphorus compounds. Saunders synthesized nerve poisons, including diisopropyl phosphorofluoridate (DFP).[11] Schrader and his co-workers found, in 1937, a contact insecticidal activity in some organophosphorus compounds of the general formula:

$$\begin{array}{c} R^1 \\ \diagdown \\ N - \overset{\overset{\displaystyle O(S)}{\|}}{\underset{\underset{\displaystyle OR^3}{|}}{P}} - Acyl \\ \diagup \\ R^2 \end{array}$$
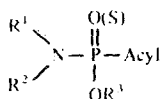
where R^1, R^2, and R^3 are alkyl groups, and "acyl" is an inorganic or organic acid radical such as Cl, F, SCN, and CH_3COO.[12] Since this point, a variety of fruitful results have been brought forth. Schrader et al. found, in 1941, a systemic insecticide, octamethylpyrophosphoramide (OMPA), which was later named schradan after its discoverer, and also discovered a number of insecticidal organophosphorus esters, including the first practical insecticide named "Bladan," which contained tetraethyl pyrophosphate (TEPP) and was marketed in Germany in 1944. The synthesis of tetraethyl pyrophosphate was first performed by Moschnine, and then by De Clemont in 1854, and was repeated by several authors, including Nylén (1930) and Arbuzov (1938), without their taking notice of its toxicity. De Clemont tasted TEPP, but did not realize its toxicity.[10]

The great advancements in agricultural practice and scientific knowledge on the structure-activity relationship of organophosphorus insecticides were achieved by the discovery of compound No. 605, named parathion, diethyl p-nitrophenyl phosphorothionate, by Schrader in 1944. Although parathion itself is extremely toxic to mammals as well as to insects, many less toxic insecticides have been developed by slight structural modifications; for instance, chlorthion,[13] fenthion,[14] and fenitrothion[15] were discovered in 1952, 1958, and 1959, respectively.

1

$(i-C_3H_7O)_2P-F$ with =O above P

DFP

$((CH_3)_2N)_2P-O-P(N(CH_3)_2)_2$ with =O above each P

schradan

$(C_2H_5O)_2P-O-P(OC_2H_5)_2$ with =O above each P

TEPP

$(C_2H_5O)_2P-O-$ (benzene ring) $-NO_2$ with =S above P

parathion

$(CH_3O)_2P-O-$ (benzene ring) $-NO_2$ with =S above P, Cl on ring

chlorthion

$(CH_3O)_2P-O-$ (benzene ring) $-SCH_3$ with =S above P, CH_3 on ring

fenthion

$(CH_3O)_2P-O-$ (benzene ring) $-NO_2$ with =S above P, CH_3 on ring
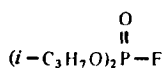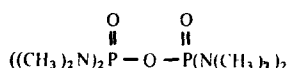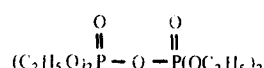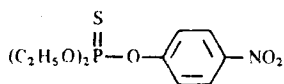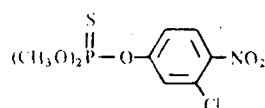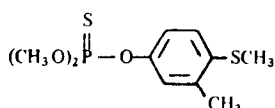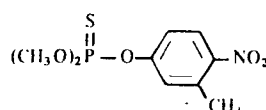
fenitrothion

All these active compounds have an acid anhydride linkage and a general formula for biologically active organophosphorus compounds first proposed by Schrader:[12]

$$R^1 \diagdown \quad P = O(S)$$
$$R^2 \diagup \quad \diagdown Acyl$$
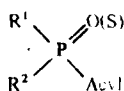
where, R^1 and R^2 = alkyl, alkoxy or amino groups, and acyl = any acid residue.

Another important compound with low mammalian toxicity, malathion, discovered by American Cyanamid Co. in 1950, has the carboxy ester group. Demeton, found in 1951 by Bayer AG, and its related compounds are important insecticides of another class, which have a thioether group and systemic insecticidal activity.

$(CH_3O)_2P-S-CHCO_2C_2H_5$ with =S above P, and $CH_2CO_2C_2H_5$ below

malathion

$(C_2H_5O)_2P-O-C_2H_4-S-C_2H_5$ with =S above P
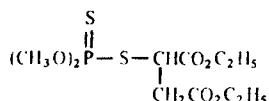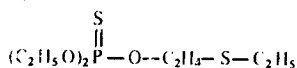
demeton-O

In 1952, the Perkow reaction was discovered,[16] and many important vinyl phosphate esters have been recently introduced as practical insecticides (see Section II.A.4).

The inhibitory activity of organophosphorus esters against cholinesterases was first found, in 1941, by Adrian and his co-workers.[17] It was found by Balls, in 1949, that the inhibition was attributable to the phosphorylation of the esteratic site. (This was initially demonstrated by the reaction of DFP with chymotrypsin.)[18] Actual thiono type insecticides do not inhibit the esterases in vitro, but their activation to potent anticholinesterases occurs in vivo. Gage demonstrated, in 1953, that the inhibitor produced from parathion in vivo was the oxo analog, paraoxon.[19] The mode of action, metabolism, and selective toxicity of organophosphorus insecticides have been actively investigated, particularly in the United States.

In addition to insecticidal and acaricidal activities, a variety of biological activities of organophosphorus compounds was discovered. Some compounds are useful as nematocides, others as anthelmintic agents. Since the fungicide, Kitazin, was discovered in 1963 in Japan,[20] a number of organophosphorus fungicides have been developed. Many of them are phosphorothiolate esters. Furthermore, herbicidal phosphorus amidoesters were also recently marketed. Plant growth regulators have also been developed, containing

phosphonic acid, phosphorotrithiolate, phosphorotrithioite, and phosphonium salt. Rodenticides were recently developed, and many aziridine derivatives of phosphoric acid are actively studied for insect chemosterilants.[21] Finally, certain organophosphorus compounds are active as antitumor agents; cyclophosphamide (Endoxan) is a typical example.[22]

Because of their relatively low persistency and high effectiveness, organophosphorus pesticides are now used widely in the world. Thus, about 140 phosphorus compounds are or were used as practical pesticides (including plant growth regulators) in the world. More than 60,000 tons a year of organophosphorus pesticides are produced in the United States alone.

For the chemistry and biological chemistry of organophosphorus compounds and pesticides, many excellent books have been published.[2,3,11,13,23-36]
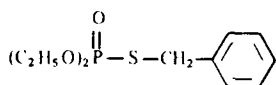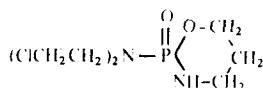
Kitazin   cyclophosphamide

B. NOMENCLATURE

The nomenclature of the organic phosphorus compounds is confusing because different countries use their own system. Some examples of different nomenclature systems adopted by Chemical Abstracts, Beilstein, Scandinavia, Kosolapoff's book,[3] and others have been shown by Fest.[2] In this book, the rules[37] established by the agreement of the British Chemical Society and American Chemical Society in 1952 are adopted.

Organophosphorus compounds are named as derivatives of the corresponding parent compounds: acids or hydrides. Some of the parents are listed below.

Hydrides	
Phosphine	H_3P
Phosphine oxide	H_3PO
Phosphine sulfide	H_3PS
Phosphorane	H_5P
Trivalent acids	
Phosphorous acid	$(HO)_3P$
Phosphonous acid	$(HO)_2PH$
Phosphinous acid	$HOPH_2$
Pentavalent acids	
Phosphoric acid	$(HO)_3PO$
Phosphonic acid	$(HO)_2HPO$
Phosphinic acid	$(HO)H_2PO$

As shown in the following examples, structures containing C-P bond(s) are named by prefixing the group name to the parent name.
Examples:

2-Chloroethylphosphonic acid	$ClCH_2CH_2PO(OH)_2$
Triethylphosphine oxide	$(C_2H_5)_3PO$

For the derivatives of acids, structures formed by the operation of replacing are named by insertion of the appropriate affix just preceding the valency suffix (-ic or -ous for acids and -ate or -ite for esters) in the parent name as shown in Table 1.

Esters are named by replacing the ending -ic or -ous acid with -ate or -ite, respectively. The esters of phosphoric acid and phosphorous acid are not specially named as phosphorate and phosphorite, but as

3

TABLE 1

Affix	Operation	Name and structure	
-amid(o)-	OH → NH$_2$	Phosphoramidic acid	(HO)$_2$P(O)NH$_2$
-chlorid(o)-	OH → Cl	Phosphorochloridic acid	(HO)$_2$P(O)Cl
-imid(o)-	=O → =NH	Phosphorimidic acid	(HO)$_3$P=NH
-thio-	OH or =O → SH or =S	Phosphorothioic acid	H$_3$PO$_3$S
-thiolo-	OH → SH	Phosphorothiolic acid	(HO)$_2$P(O)SH
-thiono-	=O → =S	Phosphorothionic acid	(HO)$_3$P=S

phosphate and phosphite, respectively. Partial esters are named by inserting the term "hydrogen" between the ester radical name and the parent name.

Chemical names of some pesticides are presented as in the examples. Common and/or trade names are also presented.

Examples:

2,2-Dichlorovinyl dimethyl phosphate, dichlorvos, DDVP
(CH$_3$O)$_2$P(O)-OCH=CCl$_2$

Dimethyl p-nitrophenyl phosphorothionate,* parathion-methyl
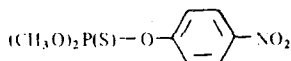
Diethyl S-(ethoxycarbonylmethyl) phosphorothiolothionate,* acethion

(C$_2$H$_5$O)$_2$P(S)SCH$_2$CO$_2$C$_2$H$_5$
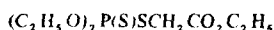
S-Benzyl diethyl phosphorothiolate, Kitazin®
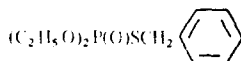
Ethyl p-nitrophenyl phenylphosphonothionate, EPN
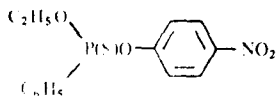
2,4,5-Trichlorophenyl diethylphosphinothionate, Agvitor
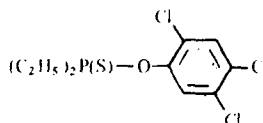
2-Chloro-4-tert-butylphenyl methyl N-methylphosphoramidate, crufomate, Ruelene®
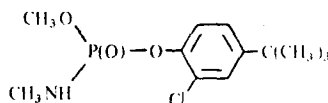
O,S-Dimethyl phosphoramidothiolate, methamidophos, Monitor®
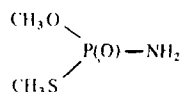
Diisopropyl phosphorofluoridate, DFP**
(i-C$_3$H$_7$O)$_2$P(O)F
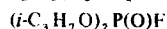
Tributyl phosphorotrithioite, merphos, Folex®
(C$_4$H$_9$S)$_3$P

The dialkyl esters of phosphorous acid exist as the esters of tautomeric phosphonic acid. Thus, they may be named phosphonates. However, they are traditionally named dialkyl phosphites.

---

*Many authors prefer to name parathion-methyl O,O-dimethyl O-p-nitrophenyl phosphorothioate. "Thioate" does not distinguish between thionate (P=S) and thiolate (P-S-). Similarly, acethion may be named as O,O-diethyl S-ethoxycarbonylmethyl phosphorodithioate.

**This is not a pesticide, but a nerve gas.

For example: dibenzyl phosphite

$$(C_6H_5CH_2O)_2P-OH \rightleftharpoons (C_6H_5CH_2O)_2\overset{\overset{\displaystyle O}{\|}}{P}H$$
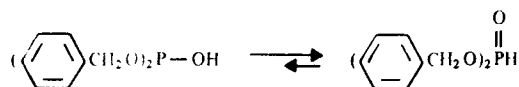
Fully operated structures no longer having acid or ester functions are named according to the Chemical Abstracts order of precedence of functions. For example:

N,N,N',N'-Tetramethylphosphorodiamidic fluoride, dimefox $((CH_3)_2N)_2P(O)F$

For compounds having more than two phosphorus atoms, no rule in the nomenclature is established. Pyrophosphoric acid may be used as a parent, as in tetraethyl pyrophosphate, TEPP.

$$(C_2H_5O)_2P(O)-O-P(O)(OC_2H_5)_2$$
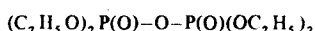
They may be named also as anhydrides, as bis-N,N,N',N'-tetramethylphosphorodiamidic anhydride, schradan.

$$((CH_3)_2N)_2P(O)-O-P(O)(N(CH_3)_2)_2$$
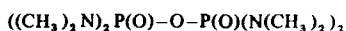
Group names including phosphorus atom are sometimes used for naming of complicated compounds. The group names may be derived from

phosphinyl	$H_2P(O)-$
phosphinothioyl	$H_2P(S)-$
phosphinimyl	$H_2P(NH)-$

as

| dimethoxyphosphinothioyloxy | $(CH_3O)_2P(S)O-$ |
| aminomethylphosphinylthio | $H_2N(CH_3)P(O)S-$ |

Actual pesticides are given as examples;

2-(Diethoxyphosphinylimino)-1,3-dithiolane, Cyolane®
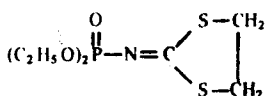
N-(Diethoxyphosphinothioyl)phthalimide, Dowco 199
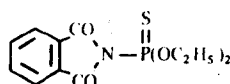
A few pesticides have a ring system containing phosphorus atom. Names of such rings are listed in Table 2.

Example:

2-Methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulfide, Salithion®
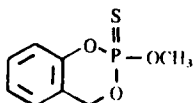
2,2,4,4,6,6-Hexakis(1-aziridinyl)-2,2,4,4,6,6-hexahydro-1,3,5,2,4,6-triazatriphosphorine, Apholate

5

TABLE 2
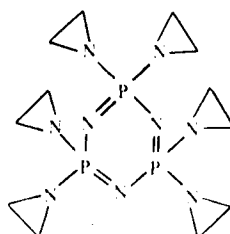
Name of Ring Systems Involving Phosphorus

Ring Size	Ring contains nitrogen		Ring contains no nitrogen	
	Unsaturated	Saturated	Unsaturated	Saturated
5	Phosphole	Phospholidine	Phosphole	Phospholane
6	Phosphorine	–	Phosphorin	Phosphorinane

The names of commercial pesticides are more confusing because of the variety of common and proprietary names. A proprietary name is always used with a capital letter and a registered trade name is followed by an ®. Common names are recommended by national or international committees. Unfortunately, different countries adopt their own common names for certain pesticides. For example, dimethyl 3-methyl-4-nitrophenyl phosphorothionate is named fenitrothion by the International Organization for Standard and British Standards Institution, while it is named metilnitrofos in the USSR, and MEP in Japan. No common name is recommended yet for this compound in the USA, where the trade name, Sumithion®, is used.

C. STRUCTURE AND SOME PROPERTIES OF PHOSPHORUS COMPOUNDS

1. Electronic Structure

Phosphorus is placed on the second row of Group V elements in the periodic table. Its properties are most suitably comparable with nitrogen. They make trivalent compounds and onium salts. The greatest difference is that phosphorus yields pentavalent compounds, as do arsenic, antimony, and bismuth.

The electronic configuration of the neutral phosphorus atom is denoted as $1s^2 2s^2 2p^6 3s^2 3p^3$. This means that the phosphorus atom has 5 valence electrons in the M-shell, 1 electron pair in the 3s-orbital, and 3 electrons in the 3p-orbitals. The activation energy to promote electron from 3s to 3p and 3p to 3d is relatively low, 7.5 and 9 eV, respectively.[25] In the case of nitrogen, having a similar electronic configuration, the corresponding activation energy from 2s to 2p and 2p to 3d is 10.9 and 12 eV, respectively. Therefore, in phosphorus compounds the d-orbital can be used much more easily for binding hybrid orbitals. This is the reason why phosphorus makes penta- or higher valent compounds.

2. Trivalent Phosphorus Compounds

Phosphorus compounds may be classified by the number of σ-bonds connected to phosphorus, as shown in Table 3.[24] Besides the listed classes of compounds which have bond numbers of 3,4,5, or 6, some singly connected, unstable phosphorus compounds, such as PN, are also known. The compounds of trivalent phosphorus exhibit the pyramidal symmetry consisting of p^3-hybridization and a certain degree of sp^3-character (Figure 1a).[24] Thus, their bond angles range between 93.5° for phosphine PH_3, and 100° for phosphorus trichloride PCl_3, instead of the theoretical 90° of a pure p^3-hybrid. These are smaller than the bond angles of corresponding nitrogen compounds, which are near the theoretical 109.5° of a pure sp^3-hybrid. This is due to the bigger radius of phosphorus (1.9 Å versus 1.5 Å of nitrogen), and to a smaller steric interaction among each substituent, because of a more extended lobe in the 3p-orbital of phosphorus than that in the 2p-orbital of nitrogen.

Phosphine PH_3 may be regarded as the parent compound of trivalent phosphorus compounds, and there are many organic phosphines derived by the replacement of the hydrogens with various alkyl and aryl groups. As another type of important organic trivalent phosphorus compounds, the esters of the following three oxyacids should be offered: phosphinous acid H_2POH, phosphonous acid $HP(OH)_2$, and phosphorous acid $P(OH)_3$.

The free acids of trivalent phosphorus undergo isomerization into tautomeric pentavalent acids

TABLE 3

Classification of Phosphorus Compounds

Number of σ-bonds	3	4		5	6
σ-Bond hybridization*	p^3 with sp^3 character	sp^3		sp^3d	sp^3d^2
Number of π-bonds	0	0	1	0	0
Number of lone pair	1	0	0	0	0
Directional characteristics*	Trigonal pyramidal	Tetrahedral		Trigonal bipyramidal	Octahedral
Examples of compounds	PCl₃ P(OR)₃	R₄P⁺	(RO)₃PO	PCl₅	PCl₆⁻

*See Figure 1.

p^3-bonding

sp^3-bonding

(a)

(b)

sp^3d-bonding

sp^3d^2-bonding

(c)
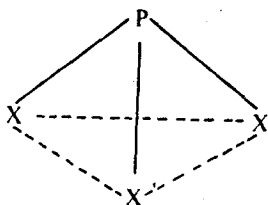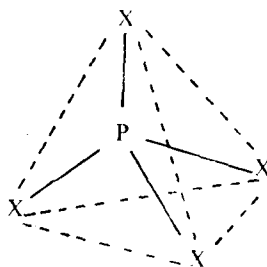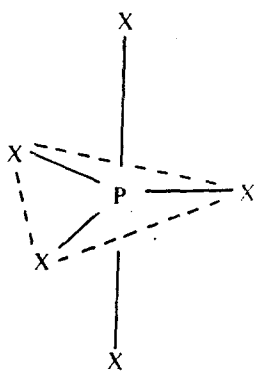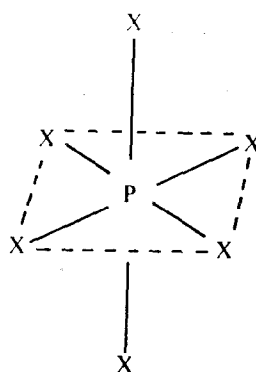
(d)

FIGURE 1. Geometry of the various types of bonding found in phosphorus compounds.

(phosphoryl form). The equilibrium is strongly towards the latter, owing to the stable phosphoryl bond (P=O).

$$\underset{HO}{\overset{HO}{>}}\ddot{P}-OH \;\longrightarrow\; \underset{HO}{\overset{HO}{>}}P\overset{O}{\underset{H}{<}}$$

This is also the case in partial acids such as dialkyl phosphites. They exist almost entirely in the phosphonate form, in a free state or neutral solution. As there is no lone pair electrons on phosphorus in the phosphonate form, dialkyl phosphites have few properties of trivalent phosphorus compounds, i.e., they show only very low nucleophilic reactivity.

$$\underset{RO}{\overset{RO}{>}}\ddot{P}-OH \;\rightleftharpoons\; \underset{RO}{\overset{RO}{>}}P\overset{O}{\underset{H}{<}}$$

They make salts, however, which behave as trivalent phosphorus compounds.

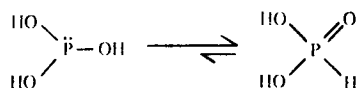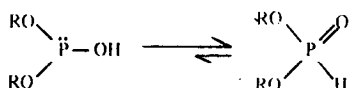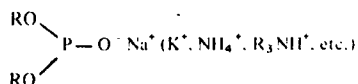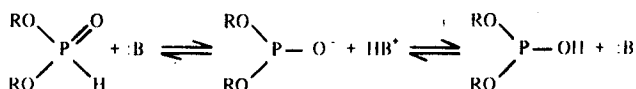$$\underset{RO}{\overset{RO}{>}}P-O^-\;Na^+\;(K^+,\;NH_4^+,\;R_3NH^+,\;etc.)$$

Moreover, the equilibrium shifts towards hydroxy form in a solvent (B) having the property of Lewis base, such as dioxane.[38]

$$\underset{RO}{\overset{RO}{>}}P\overset{O}{\underset{H}{<}}+:B \;\rightleftharpoons\; \underset{RO}{\overset{RO}{>}}P-O^-\;+\;HB^+ \;\rightleftharpoons\; \underset{RO}{\overset{RO}{>}}P-OH\;+\;:B$$

On the other hand, tri-substituted derivatives in which the tautomerism is restricted are stable.

Di- and tri-alkyl phosphites and phosphorus trichloride are very important as starting materials or intermediates for the preparation of more complicated organophosphorus compounds. Trialkyl phosphites are highly nucleophilic reagents. Although dialkyl phosphites are much less reactive, their salts are active enough as nucleophiles. Many examples of reactions applied for the preparation of organophosphorus pesticides are presented in Chapter II.

However, only a small number of phosphites, themselves, have been applied for agricultural use; dibenzyl phosphite has fungicidal activity, tris-[β-(2,4-dichlorophenoxy)ethyl] phosphite (2,4-DEP) is a herbicide, and tributyl phosphorotrithioite (merphos) is useful as a cotton defoliant.

$$(Cl-\underset{}{\overset{Cl}{\bigcirc}}-OCH_2CH_2O)_3P \qquad\qquad (C_4H_9S)_3P$$

2,4-DEP   merphos
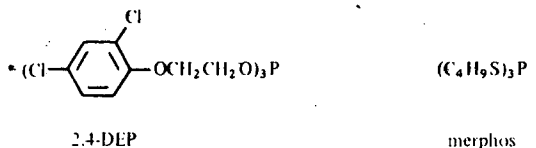
3. Phosphonium Salts

As would be expected by the analogy of amines, the compounds of triply connected phosphorus act as electron donors to yield phosphonium salts, which correspond to ammonium salts. The resulting quadruply connected phosphorus compounds are arranged tetrahedrally about the phosphorus atom, which is sp^3-hybridized as shown in Figure 1b.

The conversion of nonsubstituted phosphine PH_3, which is essentially p^3-hybridized (bond angle 93.5°),

into sp^3-hybridized phosphonium (bond angle 109°) is energetically unfavorable. Therefore, the basicity of nonsubstituted phosphine is too weak to measure the pK_b value, which was indirectly estimated at 22—28 (compare to the value 4.75 of ammonia). Thus, nonsubstituted phosphonium salts are so unstable that they decompose in water into the corresponding components.

$$H_4P^+X^- \xrightarrow{\;H_2O\;} PH_3 + HX$$
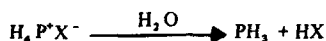
However, tertiary phosphines are much stronger bases, comparable with corresponding amines; for example the pK_b value of trimethylphosphine is 5.35, and that of the corresponding amine is 4.20. There is apparently a considerable contribution of sp^3-hybridization in tertiary phosphines, since their bond angles range around 100°, instead of the theoretical 90° for a pure p^3-hybrid. Thus, quaternary phosphonium salts are as stable as ammonium salts.

Moreover, even tetraphenyl derivatives, which do not exist as ammonium salts, are known to form phosphonium salts. This is attributed to the diminished basicity of triphenylamine, due to the resonance effect between an unshared pair of electrons on nitrogen, and the π-electrons of benzene rings, and to the steric hindrance between benzene rings. On the other hand, in the phosphorus compounds little steric hindrance is expected, owing to the larger bonding radius and negligible resonance effect due to poor $p\pi$-$p\pi$ overlapping. The poor $p\pi$-$p\pi$ overlapping is due to the more extended $3p$-orbital, as compared with the more squatty $2p$-orbital as shown in Figure 2.

Certain phosphonium salts show interesting biological activities; Phosphon (tributyl-2,4-dichlorobenzyl-phosphonium chloride) is a plant growth regulator, and some other phosphonium salts show fungicidal or herbicidal activity.

$$(C_4H_9)_3\overset{+}{P}CH_2 - \langle \text{C}_6\text{H}_3 \rangle - Cl \cdot Cl^-$$
$$\underset{Cl}{\big|}$$
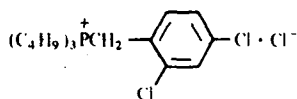
Phosphon

4. Pentavalent Phosphorus Compounds

Pentavalent phosphorus compounds may be divided into two classes by the number of σ-bonds connected to phosphorus. The majority of the compounds have four σ-bonds and one π-bond on the average for detail, see Reference. 24, Vol I, Chapter 2). A few compounds have five σ-bonds (Table 3).
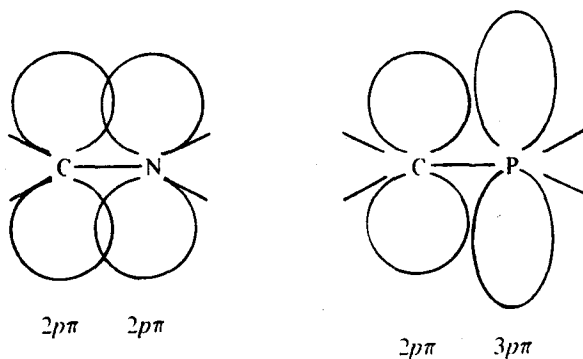

$2p\pi \quad 2p\pi$

$2p\pi \quad 3p\pi$

FIGURE 2. Distribution of $p\pi$ electrons of C, N, and P.