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Sasaki, Mitsuru

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# Current Status of Organophosphorus Insecticide and Stereochemistry

**Mitsuru Sasaki,**
Division of Bio-systems Chemistry, Graduate School of Science and Technology,
Kobe University, Kobe, Hyogo 657-8501, Japan
E-mail: msasaki@kobe-u.ac.jp

*Current status of chiral organophosphorus agrochemicals is firstly reviewed in terms of steric structure – activity relationships in insect, disease and weed control. Recent progress in the synthesis and reaction of chiral organophosphorus compounds is then described: asymmetric synthesis of organophosphorus synthetic intermediates with asymmetric induction at phosphorus center in the molecule, configuration and conformation of cyano-salithion and its derivatives, and stereochemical course in the conversion of α-aminoalkylphosphonic acids into α -hydroxyalkylphosphonic acids with nitrous acid.*

**Keywords**: chiral organophosphorus agrochemicals, steric structure – activity relationships, organophosphorus insecticides, organophosphorus fungicides, orpanophosphorus herbicides

## 1. INTRODUCTION

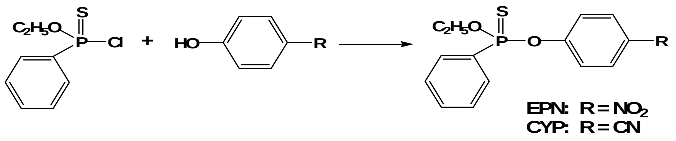
Organophosphorus agrochemicals including organophosphorus insecticide are still useful tools for crop protection. For instance, organophosphorus insecticides have been widely used in terms of their cost/performance with broad insecticidal spectra.

There are organophosphorus agrochemicals having chirality at the phosphorus or at the carbon center in the molecule. The importance of chirality in organophosphorus agrochemicals is well recognized in most aspects of their chemistry, biochemistry, biology and toxicology [1]. Thus reviewing the synthesis, selective toxicity and stereoselectivity of organophosphorus agrochemicals not only organophosphorus insecticide but also organophosphorus fungicide or herbicide will be firstly done on the following topics; absolute configuration-insecticidal activity relationships of the enantiomers of some organophosphorus insecticides, asymmetric rule on the Acetylcholine esterase (AchE) inhibition by organophosphorus insecticides, and biological activity of the optical isomers of some phosphoramidothioates and α-hydroxyethylphosphinic acid. Recent developments on the methodology for preparing optically active phosphorus compounds having biological activity will be then discussed in terms of asymmetric synthesis of organophosphorus synthetic intermediates with asymmetric induction at phosphorus center in the molecule, conformational analysis of phosphorus-containing heterocycles, and stereochemical course in the conversion of α-aminoalkylphosphonic acids to α-hydroxyalkylphosphonic acids.

## 2. Steric structure - activity relationships of some organophosphorus insecticides

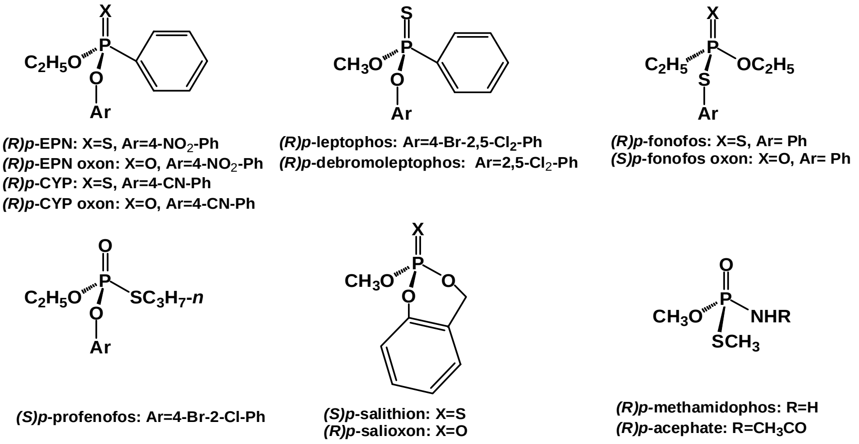
Chiral organophosphorus insecticides including phenyl phosphonates and phosphoroamidothiolates have been resolved into the optically active isomers to examine their toxicity to a variety of insects and mammals. For example, as shown in Table 1, the stereospecificity in toxicity of the enantiomers of EPN and CYP has been reported that the insecticidal activity of (*R*)-enantiomers is higher than that of (*S*)-isomers while the (*S*)-isomers have a higher potential with delayed neuropathy [2].

**TABLE 1** Stereospecificity in toxicity of the enantiomers of EPN and CYP



| | |
|---|---|
| Insecticidal Activity | (*R*)-(+)- > (*S*)-(-)- |
| Delayed Neuropathic Potential | (*S*)-(-)- >> (*R*)-(+)- |

The preferred absolute configuration of some chiral organophosphorus insecticides is predicted on the basis of the data of relationship between absolute stereostructure and AchE inhibition as illustrated in Figure 1 [3].



*(R)p*-EPN: X=S, Ar=4-$NO_2$-Ph
*(R)p*-EPN oxon: X=O, Ar=4-$NO_2$-Ph
*(R)p*-CYP: X=S, Ar=4-CN-Ph
*(R)p*-CYP oxon: X=O, Ar=4-CN-Ph

*(R)p*-leptophos: Ar=4-Br-2,5-$Cl_2$-Ph
*(R)p*-debromoleptophos: Ar=2,5-$Cl_2$-Ph

*(R)p*-fonofos: X=S, Ar= Ph
*(S)p*-fonofos oxon: X=O, Ar= Ph

*(S)p*-profenofos: Ar=4-Br-2-Cl-Ph

*(S)p*-salithion: X=S
*(R)p*-salioxon: X=O

*(R)p*-methamidophos: R=H
*(R)p*-acephate: R=$CH_3CO$

**FIGURE 1** Preferred absolute configuration of organophosphorus insecticides

Thus the more active isomer can be depicted as general formula **A**, where a smaller substituent attached to the phosphorus atom of non-leaving groups is in the backside of the paper if the leaving group is in the front and P=X bond is on the paper as shown in Figure 2. This will be an asymmetric rule of AchE inhibition by organophosphorus insecticides, compared with Schrader' acyl rule [4].

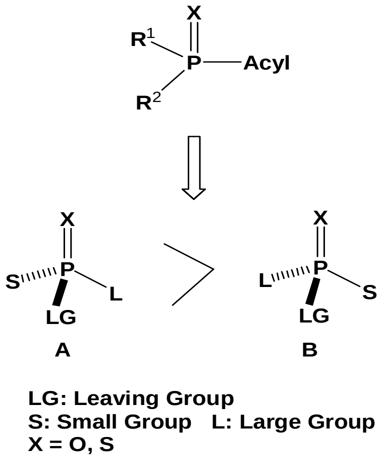
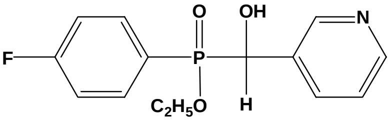


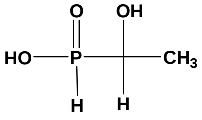
**FIGURE 2** From acyl to asymmetric rule

## 3. Steric structure - activity relationships of some organophosphorus fungicides

3-Pyridylmethylphosphonates showing antifungal activity against powdery mildew were found to inhibit strongly ergosterol biosynthesis [5].



**1**



**2**

**FIGURE 3** Chiral organophosphorus fungicides

The phosphinate **1** in a *threo* form is more effective for controlling powdery mildew than that in an *erythro* form. α-Hydroxyethylphosphinic acid **2** having antifungal activity against *Phycomycete* pathogens is perhaps the closest phosphorus analog of lactic acid. The (*S*) - enantiomer of the phosphinic acid is more antifungal, whereas the (*R*) -

enantiomer with high acute toxicity is much more phytotoxic [6]. This finding clearly demonstrates the advantage of utilizing the optical isomer in practice.

## 4. Steric structure – activity relationships of some organophsphorus herbicides

There are a few reports on the stereochemistry – herbicidal activity relationship of chiral organophosphorus agrochemicals. For example, The (-) – enantiomers of DMPA **3** and S-2571 **4** were found to be more herbicidal than their antipodes without any information on the absolute configuration [7]. Phosphinothricin **5** having a stereogenic center at the α-carbon atom in the molecule is an active ingredient of herbicidal antibiotics [8].

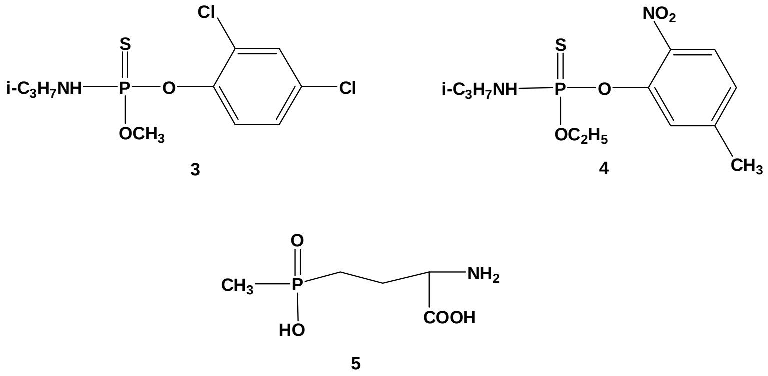


**FIGURE 4** Chiral organophosphorus herbicides

## 5. Asymmetric synthesis of organophosphorus synthetic intermediates with asymmetric induction at phosphorus center in the molecule

As described above, it is apparent that the use of organophosphorus agrochemicals as optically active forms is more advantageous than that of racemic forms in terms of biological efficacy, toxicological and even environmental problem. However, so far, there is no optically active form at the phosphorus center in the molecule among commercialized chiral organophosphorus agrochemicals, mainly because of the lack of a practical method for realizing mass production of optically active phosphorus compounds. One resolution for the mass production will be to devise an asymmetric synthesis based on the asymmetric induction at phosphorus center in the molecule.

For this purpose, an approach to the optically active phenylphosphinates has been reported on asymmetric induction at the phosphorus center in the esterification of chiral ammonium salts of phenylphosphinic acid **6** with ethyl chloroformate leading to O-ethyl phenylphosphinate **7** [9].

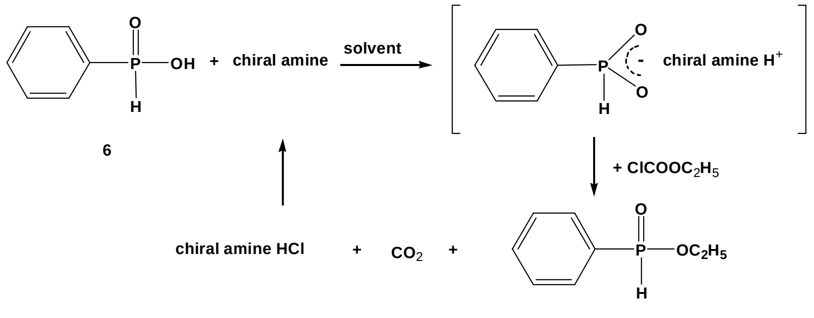


**FIGURE 5** Asymmetric synthesis of *O*-ethyl phenylphosphinate

If the chloroformate can differentiate one of two oxygens in chiral salts, the phosphinate **7** can be obtained in an optically active form, from which it may be possible to make *O*-ethyl phenylphosphonothioic acid leading to the optical isomers of EPN and CYP. So far the enantiomeric excess of the produced phosphinate **7** is up to 21.5% in the case of using *N*,*N*-dimethyl-1-naphthylethylamine as an optically active tertiary amine.

## 6. Configuration and conformation of cyano-salithion and its derivatives

Salithion: 2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulfide, is the first commercialized insecticide having phosphorus heterocycles [10]. Its 2-methoxy-4-cyano-derivative (**8**, X=S) has been reported that the heterocyclic ring is in a distorted half-chair form on the basis of X-ray crystallographic analysis, just like that of salithion, while the heterocyclic ring of both the 2-ethyl-4-cyanoderivative (**9**, X=S) and the 2-methylamino-4-cyanoderivative (**10**, X=S) is in a distorted half-boat form [11].

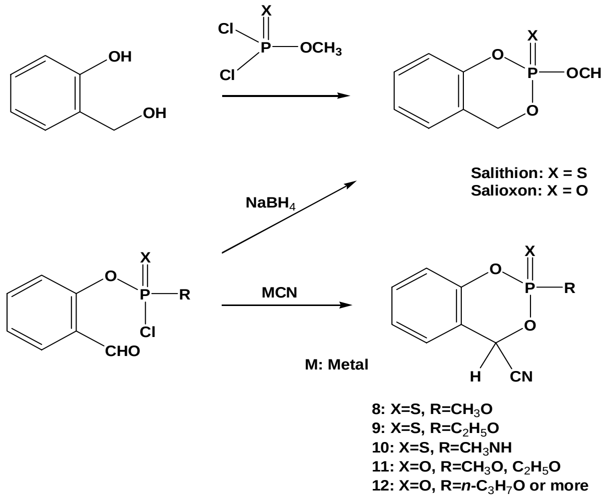


**FIGURE 6** Synthesis of salithion and its cyano derivatives

Interestingly, in a series of 2-alkoxy-4-cyanoderivatives (X=O), the conformation of the heterocyclic ring is changed with the size of 2-alkoxy group. The heterocyclic ring of 2-methoxy or 2-ethoxy-4-cyanoderivative (**11**, X=O, R=$CH_3O$ or $C_2H_5O$) is in a distorted half-chair form, while that of 2-propoxy or more 4-cyanoderivatives (**12**, X=O, R=$n$-$C_3H_7O$ or more) is in a distorted half-boat form. The origins of the conformational preferences might be attributed to the differences in intramolecular electrostatic interactions, intramolecular orbital interactions, and the lone pair effect.

## 7. Stereochemical course in the conversion of α-aminoalkylphosphonic acids into α-hydroxyalkyl-phosphonic acids with nitrous acid

Several α-amino (or hydroxy) alkyl phosphonic acids as well as the phosphinic acid show an interesting biological activity, as shown in Figure 7.

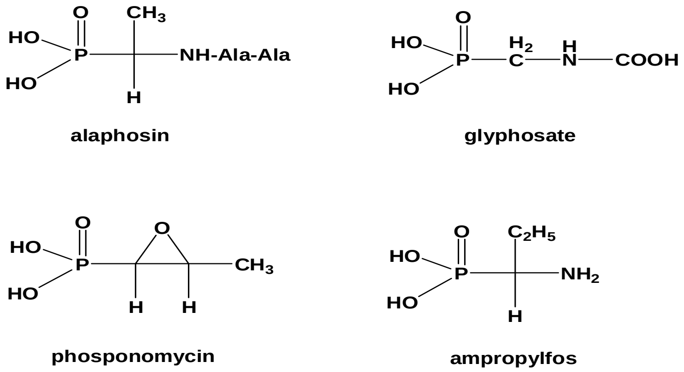


**FIGURE 7** Biological activities of some phosphonic acids

For instance, ampropylfos: α-aminopropylphosphonic acid possesses antifungal activity against some pathogens. Our interest in the conversion of α-amino group to α -hydroxy group with ampropylfos led to examining the stereochemical course at the α- position, in connection with the conversion of α-aminoalkylcarboxylic acid into the corresponding α-hydroxyalkylcarboxylic acid. Reaction of α-aminoalkylcarboxylic acids **13** with aqueous nitrous acid has been reported to proceed with double inversion at the α -position to afford the corresponding α -hydroxyalkylcarboxylic acids **16**, as shown in Figure 8 [12].

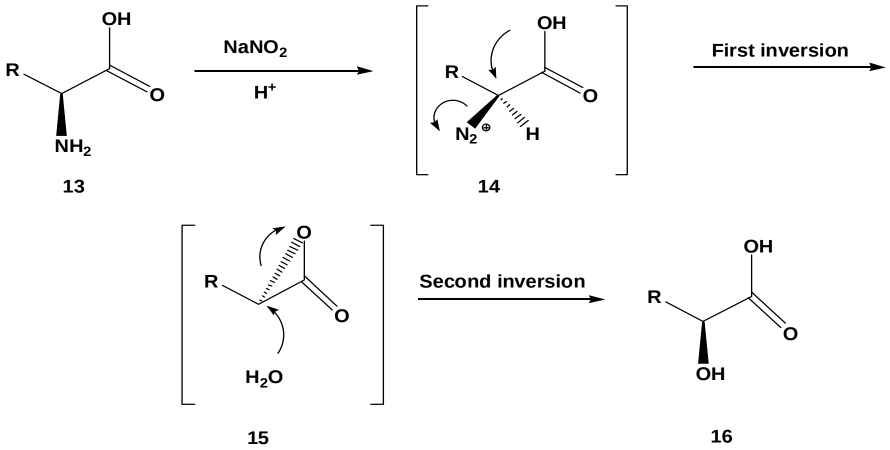
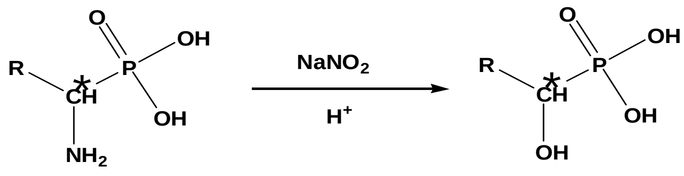


**FIGURE 8** Stereochemical course in the reaction of α-aminoalkylcarboxylic acids with nitrous acid.

The oxygen of the adjoining carboxylic acid in the first intermediary diazo-compound **14** attacks from the backside of the α-carbon with the loss of nitrogen gas to form α -lactone **15** with the inversion of configuration at the α-carbon. Subsequent hydrolysis of the second intermediary lactone proceeds again with the inversion of configuration at the α-carbon to give α-hydroxyalkylcarboxylic acids **16** which has the same configuration as that of starting α-aminoalkylcarboxylic acids **13** at the α-carbon.

A preliminary study on the conversion of optically active α-amino to α -hydroxyalkylphosphonic acids using a nitrous acid as a diazotizing agent wascarried out to diazotizate the α-aminoalkylphosphonic acids with sodium nitrite in a diluted hydrochloric acid solution.



**17**: R=$CH_3$
**18**: $C_2H_5$
**19**: $n$-$C_5H_{11}$
**20**: R=$i$-$C_3H_7$

**21**: R=$CH_3$
**22**: $C_2H_5$
**23**: $n$-$C_5H_{11}$
**24**: R=$i$-$C_3H_7$

**FIGURE 9** Conversion of α-aminoalkylphosphonic acids to α-hydroxyalkylphosphonic acids

The used optically active α-aminoalkylphosphonic acids **17** ~ **20** were R: methyl, ethyl, isopropyl, and *n*-amyl group. When (*R*)-(-)-α-aminopropylphosphonic acid was reacted with sodium nitrite in 3% HCl solution, the corresponding α -hydroxypropylphosphonic acid was obtained in good yield. The hydroxypropylphosphonic acid was esterified with diazomethane to give dimethyl α -hydroxypropylphosphonate in a quantitative yield. The phosphonate obtained was submitted to analyze its enantiopurity using chiral shift agent in $^1$HNMR spectroscopy. In the reaction of the aminoalkylphosphonic acids **17** ~ **19** having R: $CH_3$, $C_2H_5$ and n-$C_5H_{11}$ groups with nitrous acid, the hydroxyalkylphosphonic acids **21** ~ **23** having same configuration at α-position was predominantly obtained, whereas in the case of **20** R: $i$-$C_3H_7$ group the corresponding hydroxyalkylphosphonic acid **24** showed the opposite configuration at α-position.

## 8. CONCLUSION

There are chiral organophophorus agrochemicals widely used without being in an optically active form in spite that its use as the optical isomers is more advantageous than that of racemic ones. As already described, this may be mainly due to the lack of efficient methods for preparing the optical isomers on an industrial scale. A few studies have been tried to devise a more practical method for mass production of the optically active phosphorus compounds. However, developing the asymmetric synthesis of phosphorus compounds with asymmetric induction at the phosphorus center is a still challenging area of research.

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