Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA in

Scienze Chimiche

Ciclo XXIII

Area 03 Scienze Chimiche- CHIM/06- Chimica Organica

ABIOTIC AND PREBIOTIC PHOSPHORUS CHEMISTRY

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Esame finale anno 2011

Summary

Part 1

GENERAL

Chapter 1

GENERAL INTRODUCTION ON PHOSPHORUS CHEMISTRY

1.1 Organophosphorus Chemistry

Phosphorus can form bonds with many other elements. It can also form bonds with varying number of atoms (Coordination Number), which can vary from 1 to 6 and more. Also it can have different valencies, either 3 or 5. Also it has empty d-orbitals which readily accept electrons from any good donors.

Organophosphorus compounds are chemical compounds containing carbon-phosphorus bonds. Organophosphorus chemistry is the corresponding science exploring the properties and reactivity of organophosphorus compounds.[1] Common examples of those compound are reported in Figure 1.1.

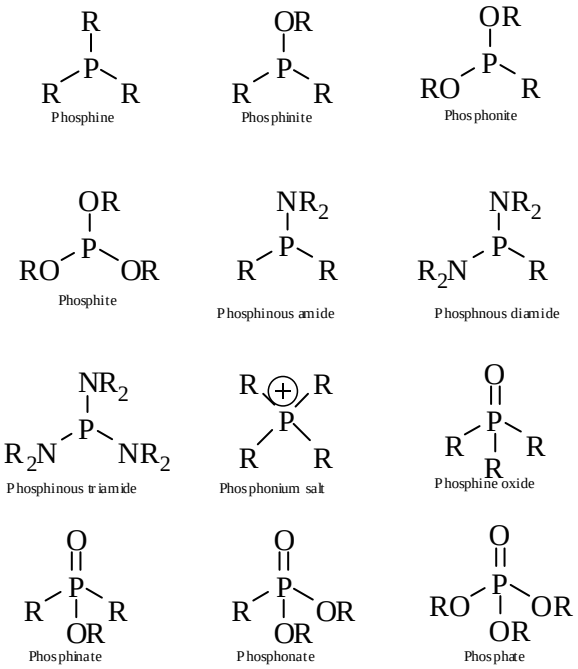


Figure 1.1 Examples of organophosphorus compounds.

The thermal stability of the P-C bond is quite high. The heat of dissociation of the 4-coordinated C-P bond is generally accepted to be about 65 Kcal/mol, and there is never any difficulty in handling most aryl and alkyl phosphorus compounds even at moderate temperatures.[2a]

1.1.1 Phosphines

Phosphanes or phosphines have oxidation state −3 and can be primary (RPH_2), secondary (R_2PH) or tertiary (R_3P). An often used organic phosphine is triphenylphosphine. Like amines, phosphines have a trigonal pyramidal molecular geometry although with larger angles. The C-P-C bond angle is 98.6° for trimethylphosphine increasing to 109.7° when the methyl groups are replaced by *tert*-butyl groups. The barrier to inversion is high for a process like inversion to occur and therefore phosphines with three different substituents can display optical isomerism.[2b]

Synthetic procedures for phosphines are:[3]

- Nucleophilic displacement of phosphorus halides with organometallic reagents such as Grignard reagents.
- Nucleophilic displacement of metal phosphides, generated by reaction of potassium metal with phosphine, as in sodium amide with alkyl halides.
- Nucleophilic addition of phosphine with alkenes in presence of a strong base (often KOH in DMSO), Markovnikov's rules apply. Phosphine can be prepared in situ from red phosphorus and potassium hydroxide. Primary (RPH_2) and secondary phosphines (R_2PH) do not require a base with electron-deficient alkenes.
- Nucleophilic addition of phosphine or phosphines to alkynes in presence of base. Secondary phosphines react with electron-deficient alkynes without base.
- Radical addition of phosphines to alkenes with AIBN or organic peroxides to give anti-Markovnikov adducts.

Oxidation has been a major obstacle when working with trivalent phosphorus as phosphines. Especially alkyl-substituted phosphines oxidize readily in air making elaborating and handling of such compounds tedious. For this reason, usually phosphines are oxidized into stable compounds after their preparation, obtaining phosphine oxide, sulfide, selenide (less common) or borane complexes derivatives.[4]

- *Phosphine oxides* are obtained by simple treatment of free phosphine with an oxidizing agent such as H_2O_2[5], O_2,[4b] *t*-BuOOH,[6] *m*-CPBA[7] (Reduction by $PhSiCl_3$,[8] $HSiCl_3$[9] with retention of configuration or $LiAlH_4$ that causes racemization).

- *Phosphine sulfides and selenides* are obtained from phosphine oxidized by elementar sulfur or selenium (Reduction by Si_2Cl_6 with retention of configuration or $LiAlH_4$ that causes racemization). [10]
- *Phosphine borane complexes* are obtained by mixing phosphines with BH_3.THF or $BH_3.Me_2S$ (decomplexation by amines, such as Et_2NH or morpholine with retention of configuration).[11]

The main reaction types of phosphines are: [3]

- as nucleophiles for instance with alkyl halides to phosphonium salts.
- as reducing agents:

Phosphines are reducing agents in the Staudinger reduction converting azides to amines and in the Mitsunobu reaction converting alcohols into esters. In these processes the phosphine is oxidized to phosphine oxide.

1.1.2 Phosphonates

Phosphonates have the general structure $R-P(=O)(OR)_2$. They have many technical applications and bisphosphonates are a class of drugs.
All bisphosphonate drugs share a common P-C-P "backbone":

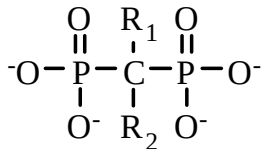


Figure 1.2 typical backbones of bisphosphonate drugs

The two PO_3 (phosphate) groups covalently linked to carbon determine both the name "bisphosphonate" and the function of the drugs. The long side chain (R_2 in the diagram) determines the chemical properties, the mode of action and the strength of bisphosphonate drugs. The short side chain (R_1), often called the 'hook,' mainly influences chemical properties and pharmacokinetics.[12]

1.1.3 Phosphites and Phosphates

Phosphite esters or phosphites have the general structure $P(OR)_3$ with oxidation state +3. Phosphites are employed in the Perkow reaction and the Arbusov reaction. Phosphate esters with the general structure $P(=O)(OR)_3$ and oxidation state +5 are of great technological importance as flame retardant

agents and plasticizers. Lacking a P−C bond, these compounds are technically not organophosphorus compounds.[3]

1.2 Uses of Organophosphorus Compounds

Organophosphorus compounds, have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators.[13] They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma. [14] In academic research organophosphorus compounds find important application in organic synthesis (Wittig, Mitsunobu, Staudinger, organocatalysis etc.).[15] The use of organophosphorus compounds as achiral or chiral ligands for transition metal-catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production.[16] Furthermore, organophosphorus compound, can be used as flame retardants for fabrics and plastic plasticising and stabilising agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors.

1.2.1 Agricultural Applications

Over the years, many organophosphorus compounds have been made and used in very large quantities in agriculture, not only as insecticides but also later as herbicides and in other applications. Phosphorus compounds have distinct advantages in the pesticides market; they are relatively easy to make, and they biodegrade readily by hydrolysis, so that the problems of residual activity, so serious with the chlorinated hydrocarbon pesticides, are avoided.
The active compounds are normally esters, amides, or thiol derivatives of phosphoric or phosphonic acid:

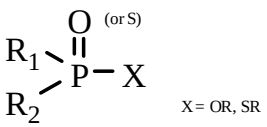
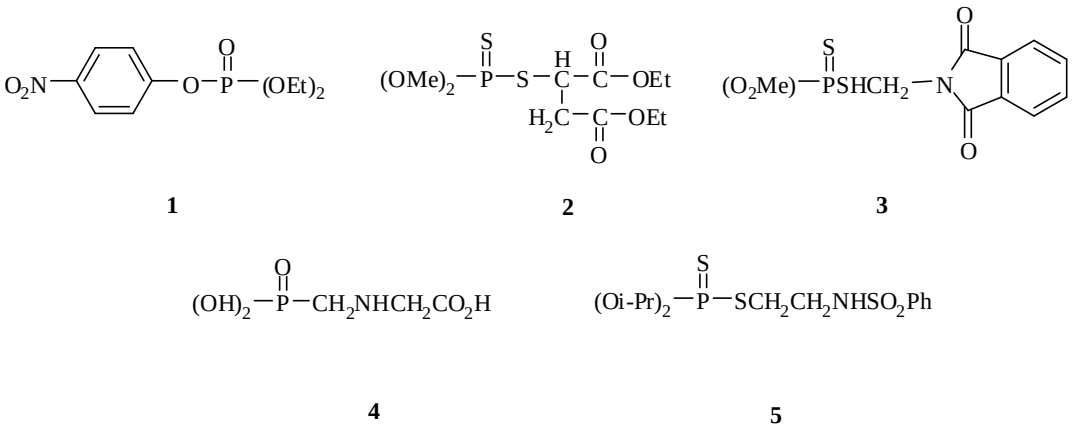


Figure 1.3 Structure of derivatives of phosphoric or phosphonic acid

Where R_1 and R_2 are usually simple alkyl or aryl groups, both of which may be bonded directly to phosphorus (in phosphinates), or linked via -O-, or -S- (in phosphates), or R_1 may be bonded directly and R_2, bonded via one of the above groups (phosphonates).

Parathion (**1**) was one of the first commercially produced insecticides; its toxicity (LD_{50}) is 55 mg/Kg, which is rather low but still requires careful handling and application in the field. It was very popular in 1960s, but after this period the interest in Parathion has greatly declined with the introduction of safer agents. Definitely, many compounds are now produced that are relatively harmless to humans yet with excellent toxicity to insects for example the well-known garden insecticide Malathion (**2**) and Phosmet (**3**) with LD_{50} up 4000 mg/Kg (Figure 1.4).



1 **2** **3**

4 **5**

Figure 1.4 Examples of some insecticides and herbicides based on organophosphorus compounds.

On the other hand, the phosphorus compounds were late entries in the fields of organic herbicides, and to this date only a few compounds have attained major commercial importance. Glyphosphate (**4**) was the first discovered and is still used (Figure 1.4). Its is known to act by the inhibition of the plant enzyme 5-enolpyruvoyl-shikimate-3-phosphate synthetase, which is involved in the biosynthesis of aromatic aminoacids and other aromatic compounds in plants. Many other phosphorus compounds show herbicidal activity, and much current research effort is going on in this area. In addition to the phosphorus-containing amino acid derivatives, other structural types are of interest, such as is seen in Betasan (**5**) (Figure 1.4).

1.2.2 Catalysis

Between various types of enantiomerically pure ligands used for catalytic asymmetric reactions, chiral tertiary phosphines have established their position as the most effective ligands for most homogeneous transition-metal catalyses.

Homogeneous asymmetric hydrogenation started with modest results (ee 15%) in 1968 using chiral monophosphine **6** (MPPP) (Figure 1.5) as ligand.[17] Neomenthyldiphenylphosphine **7** (NMDPP) and

menthyldiphenylphosphine **8** (MDPP) were prepared in 1971 by Morrison *et al*,[18] giving up to 61% ee in some cases. Knowles *et al* also published some interesting results in 1972 (ee 90%) with chiral phosphines **9** (PAMP) and **10** (CAMP)[19] At the same time alkyldimenthylphosphines **11** were used by Wilke, Bogdanovic *et al*. as ligands of nickel complexes in the catalysis of alkene codimerization and alkene-1,3-dienes codimerization.[20] In 1971-1972 we demonstrated that a chelating chiral C2-symmetric diphosphine **12** (DIOP) without asymmetric phosphorus atoms was an excellent enantioselective catalyst (ee 88%).[21] A multitude of chelating diphosphines are presently known (of C1 or C2-symmetry), some of them are patented because of industrial applications.[22] One of the most effective chiral biphosphine ligands is BINAP **13**,[23] which has exhibited its high enantioselectivity in several asymmetric reactions including rhodium- or ruthenium-catalyzed hydrogenation. Another important class of chelating biphosphine ligand is ferrocenylbiphosphines BPPF-X **14**,[24] which had been demonstrated to be effective for palladium-catalyzed allylic substitution reactions, gold- or silver-catalyzed aldol reactions, and so on.

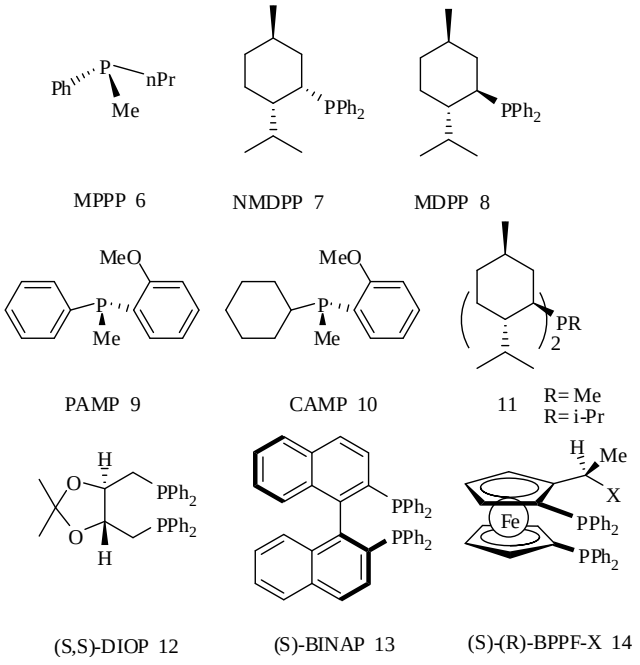


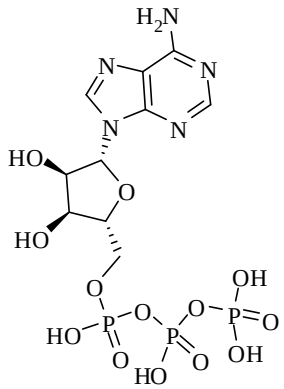
Figure 1.5 Examples of ligands for homogeneous catalysis.

1.2.3 Phosphorus in Biological Compounds

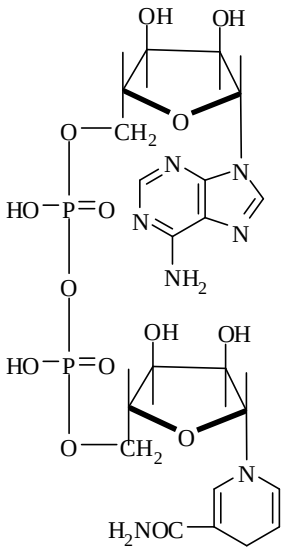
Phosphorus is present in plants and animals. There is over 454 grams of phosphorus in the human body. It is a component of fundamental living compounds. It is found in complex organic compounds in the blood, muscles, and nerves, and in calcium phosphate, the principal material in bones and teeth. Phosphorus compounds are essential in the diet. Organic phosphates, ferric phosphate, and tricalcium

phosphate are added to foods. Especially, phosphoric acid is essential in many biological derivatives such as nucleotides, nucleic acids, phospholipids and sugar phosphates.

Nucleotides are monomers consisting of a phosphate group, a five carbon sugar (either ribose or deoxyribose) and a one or two ring nitrogen containing base.
Nucleotides are the monomers of nucleic acids, with three or more bonding together in order to form a nucleic acid. The genetic material (DNA) is a polymer of four different nucleotides. The genetic information is coded in the sequence of nucleotides in a DNA molecule. Nucleotides and related compounds are also important "energy carrying" compounds. Among the ones commonly encountered are ATP (**20**), and NADH (**21**) (Figure 1.7).[25a]



adenosine triphosphate ATP **20**

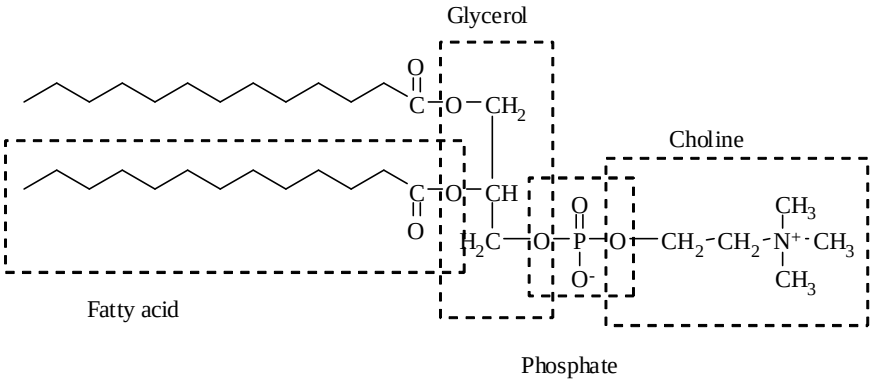


Nicotinamide adenine dinucleotide dehydrogenase
NADH **21**

Figure 1.7 Structures of ATP and NADH.

Certain phosphoric acid derivatives play a major role in driving some processes by "energy release" that accompanies the cleavage of a phosphate group and transfer to a nucleophilic substrate. The best known of the "energy-rich" phosphates is adenosine triphosphates ATP (**20**, Figure 1.7), which can transfer the terminal phosphate group to a substrate with the release of significant energy.[2c]
Actually the phosphoryl group transfer mechanism, in "energy-rich" phosphate substrates, is explained by intervention of pentacoordinated phosphorus in the transition state species. In particular the formation of cyclic pentacoordinated phosphorus species on the reactive phosphate group facilitate the attainment of the required transition state or intermediate allowing to obtain a fast and selective reaction.[26]

A phospholipid molecule consists of a hydrophilic polar head group and a hydrophobic tail (**22** figure 1.8). The polar head group contains one or more phosphate groups. The hydrophobic tail is made up of two fatty acyl chains. When many phospholipid molecules are placed in water, their hydrophilic heads tend to face water and the hydrophobic tails are forced to stick together, forming a bilayer. Phospholipids are a major component of all biological membranes, along with glycolipids and cholesterol.[26b]



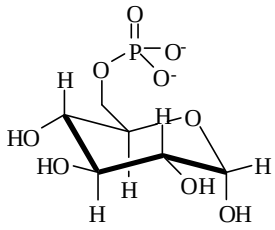
22

Figure 1.8 Typical structure of phospholipids.

Sugar phosphates are present in the human body as intermediates in the many important processes like glucose metabolism. One example is the glucose 6-phosphate **23** (figure 1.9).

It is glucose sugar phosphorylated on carbon 6. This compound is very common in cells as the vast majority of glucose entering a cell will become phosphorylated in this way. Because of its prominent position in cellular chemistry, glucose 6-phosphate has many possible fates within the cell. It lies at the start of two major metabolic pathways: the Glycolysis and Pentose phosphate pathway

In addition to these metabolic pathways, glucose 6-phosphate may also be converted to glycogen or starch for storage. This storage, in the form of glycogen, is in the liver and muscles for most multicellular animals, and in intracellular starch or glycogen granules for most other organisms.[26c]



glucose-6-phosphate **23**

Figure 1.9 Structure of glucose 6-phosphate.

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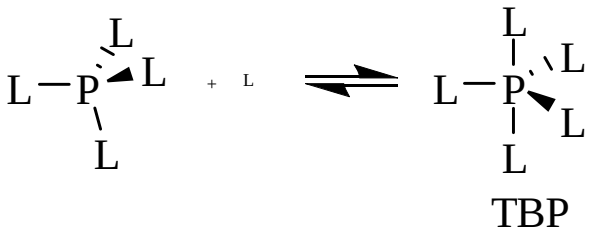
Chapter 2

THE HYPERCOORDINATE STATES OF PHOSPHORUS

One of the special properties of phosphorus that is of importance is its ability to accept more than the usual complement of 8 bonding electrons, thus acquiring 5-coordinate character with 10 electrons, or 6-coordinate with 12 electrons. This property of phosphorus was not firmly established until 1948, when the compound Ph_5P was synthesized and characterized by Wittig and Rieber.[1] Now there are many compounds known with this structural feature, which is also known to appear frequently in reactions mechanism as a transient intermediate or transition state. [2]

2.1 The 5-Coordinate State of Phosphorus

Phosphorus can undergo rapid and reversible changes between a four-coordinate and a five-coordinate state (Scheme 2.1). The preferred skeletal geometries of this states correspond to the tetrahedron and the trigonal bipyramid (TBP), respectively.[2]



Scheme 2.1 conversion between a four-coordinate and a five-coordinate state.

Molecules with five-coordinate phosphorus are essential to life[3] and the recognition of the role played by the five-coordinate state of the element in biochemistry has spurred interest in this field. On this basis, a consistent interpretation has been made of a number of significant problems of biochemistry,[4] for example: the transfer of the terminal phosphoryl group from adenosine triphosphate to

nucleophiles under basic conditions; the enzymatic transformation of mevalonic acid into isopentyl diphosphate by ATP and metal ions or the role of ATP in the biological reduction of nitrogen to ammonia (nitrogen-fixation).

Pentacoordinated phosphorus compounds are not only present as reaction intermediates in biological reactions or chemical reactions as Arbusov, Perkov and Wittig,[4b] but they can be isolated as stable compounds.[5]

2.2 Pentacoordinated structures and their non rigid character

The development of structural principles for pentacoordinated species, was centered on the trigonal bipyramid geometry. These principles have been applied with considerable success in the construction of reaction intermediates. The systematic application of mechanistic criteria for postulating the most likely pentacoordinated intermediates has led to a consistent rationalization of a large number of information on phosphorus reactions. Certain principles emerged that govern conformational preferences regarding the positioning of ligands in a TBP structure. They are listed as follows in order of importance:[6]

1. Four- or five-membered cyclic systems preferentially span axial-equatorial positions;
2. The most electronegative ligands preferentially occupy axial sites;
3. P-bonding donor ligands, in general, are positioned at equatorial sites.
4. Steric effects are minimized by locating bulky groups un equatorial position

The stability of phosphoranes (pentavalent phosphorus) is markedly increased by the presence of four- and five-membered rings, and to a lesser extent, by six-membered rings, since cyclization decreases intramolecular crowding relative to the comparable acyclic situation.[7] This assistance from intramolecular growing can outweigh any strain resulting from the deformation of bond angles within the ring. Nevertheless, ring-strain rather than intramolecular crowding is the main factor in determining the stability of tetracoordinate phosphorus. Consequently, a five membered cycle loses in stability while the corresponding cyclic phosphorane gains in stability relative to the corresponding compounds in which the phosphorus is not incorporated in rings.[8] These is thermodynamic and kinetic advantage in adding a nucleophile such as alkoxide or water to four-coordinate phosphorus to form a phosphorane intermediate when a five-membered ring is present in the phosphate, or when such a ring is easily formed during a reaction. This is in accord with Westheimer and co-workers[7,9] found studying the acid hydrolysis of cyclic esters, in fact their experimental results reported that a

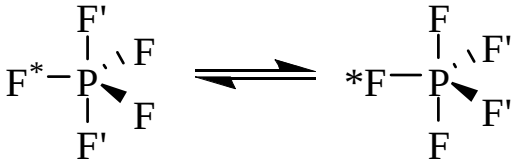
five-membered cyclic phosphate esters hydrolyze much more rapidly (10^6-10^8 times) than their open chain analogous in either acid or base.

2.3 Permutational isomerization

The permutational isomerization of the phosphoranes can occur by bond deformations (regular process) and by bond breaking and recombinations (irregular process). The regular permutational isomerizations of acyclic phosphanes can take place by either Berry pseudorotation[10,11] (BPR) or turnstile rotation[10b,11,12] (TR) or by both of these mechanism.

2.3.1 Berry pseudorotation

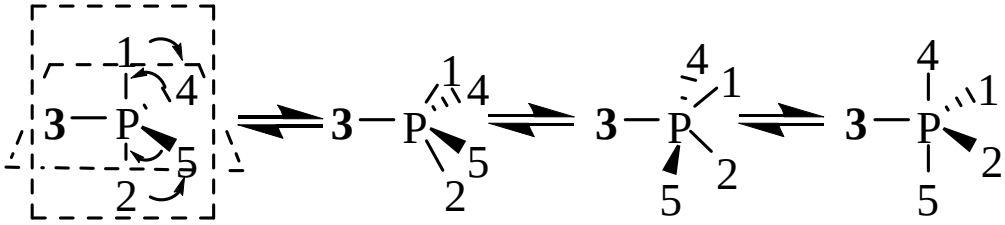
In 1960, R. S. Berry[10] suggested that the position exchange of the fluorine atoms of PF_5 occurs by a regular bond-deformation mechanism which he called pseudorotation (scheme 2.2).



Scheme 2.2 Exchange of the fluorine atoms of PF_5, consequence of BPR.

In general, this Berry pseudorotation (BPR) can be described as shown in Scheme 2.3. A pair of equatorial ligands, for instance 4 and 5, move in a plane and the two apical ligands move in another plane, perpendicular to the first. The fifth ligand, the pivot (3), does not move at all. The synchronous expansion of the original 120° diequatorial angle 4-P-5 leads to an angle of 150° in the idealized barrier situation; this angle reaches 180° in the new TBP. Similarly, the synchronous contraction of the original 180° diapical angle 1-P-2, leads to 150° in the idealized barrier situation and 120° in the new TBP. During this bending motions, the bond distances adjust to the new TBP skeletal arrangement. After the BPR, the new TBP is oriented as if the entire molecule had rotated by 90° about the pivotal bond, even though, in fact, neither a rotation of the whole molecule, and not a rotation of a ligand subsisted, for this reason the name rotation.[11]

Therefore in other words, the BPR mechanism realizes of two apical and two equatorial ligands, and the retention of the equatorial position of the pivot.



Scheme 2.3 Berry pseudo rotation with ligand 3 as pivot.[11]

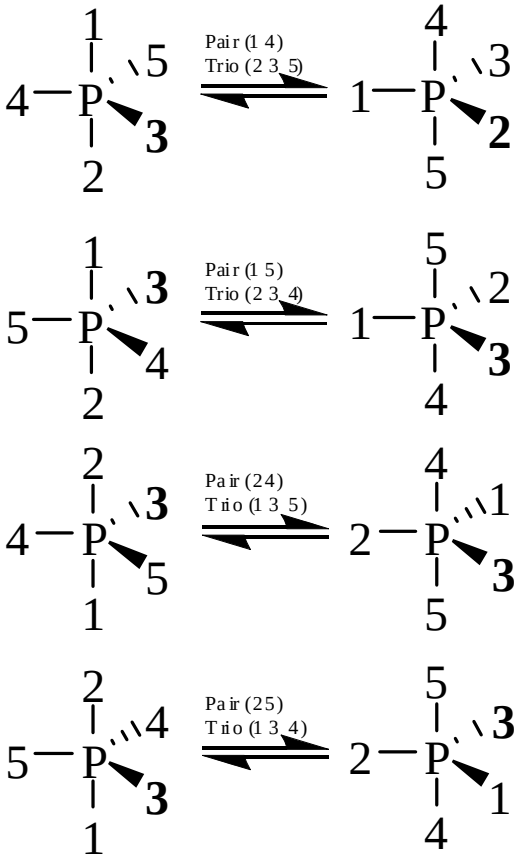
2.3.2 Turnstile rotation

About 10 years later than the Berry pseudo rotation was formulated, another theory was proposed, the turnstile rotation[12] (TR). The turnstile rotation consist in a permutation of the ligands among skeletal positions of the TBP which, in general takes the form shown in scheme 2.4.

The first TR process of scheme 2.4 corresponds to the ligand permutation (1 4) (2 3 5), which means ligand 1 replaces ligand 4 and ligand 4 replaces ligand 1, while ligand 2 replaces ligand 3, 3 replaces 5 and 5 replaces 2. The second, third and fourth equivalent TR processes correspond, respectively, to the ligand permutations (1 5) (2 3 4), (2 4) (1 3 5), (2 5) (1 3 4). It should be noted that the five ligands have been partitioned into a pair, which always contains one apical and one equatorial ligand and a trio.[11]

Obviously, the TR and the BPR processes correspond to different types of permutations of the ligands among the skeletal positions of the TBP, but the same isomerization of it can be achieved by one BPR process or by four TR process.

The differences between the two processes in the case of certain acyclic phosphoranes are not so evident, this means that the potential surface for permutational isomerization does not contain high barriers between the BPR barrier model and the TR barrier model.[10b] When two or more ligands participate in cyclic structures, the situation changes. In fact, for regular isomerizations of acyclic phosphoranes existed two mechanistic possibilities, BRP and TR, but for the case of regular isonerizations of cyclic phosphanes the only mechanistic possibility is the TR process, with the four- and the five-membered ring always as the pair of the TR pair-trio combination.



Scheme 2.4 Four equivalent turnstile processes showing the pairs and trios of ligands which effects the same isomerization as Berry pseudorotation with ligand 3 as pivot.[11]

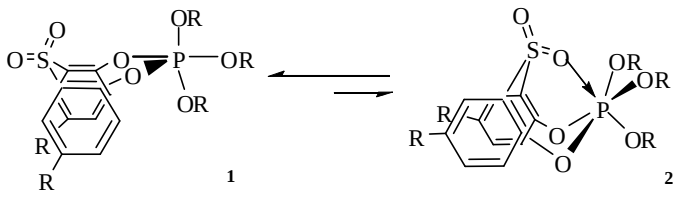
2.4 The 6-Coordinate State of Phosphorus

The chemistry of hexacoordinated phosphorus compounds has received much less attention than that of the pentacoordinated state. In recent years many stable compounds have been made in which phosphorus has six attached groups.[13,14] In general the octahedral structure, with two apical and four equatorial bonds, is adopted. In this coordination state, phosphorus is known in neutral, anionic and cationic forms. Many of the known compounds can be considered as Lewis salts obtaining from the interaction between a donor group (neutral or ionic) with five-coordinated phosphorus.

Some of the concepts of the five-coordinate state are useful also in six-coordinate state. As Muetterties and Mahler[15] showed highly electronegative elements, in particular fluorine, stabilize the hexacoordinated state and their prefer the apical position. Fluxional character can be present,[16] and ^{31}P NMR shift are usual found at high field.

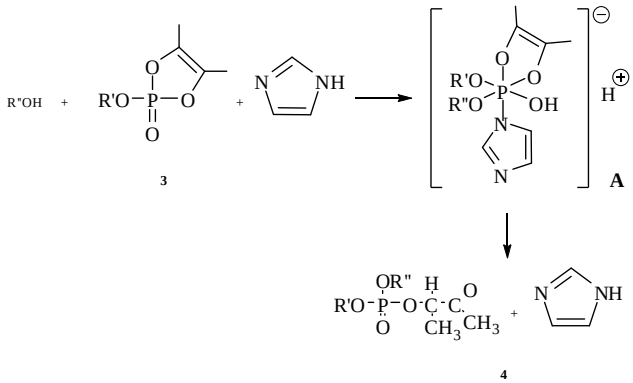
Six-coordinate compounds are receiving attention at present because they are recognised as transient intermediates in certain reactions of five-coordinate structures, adding a new dimension to considerations of reaction mechanisms. Generally, it is considered that pentacoordination to

hexacoordination occurs through a square pyramidal (SP) geometry from a trigonal bipyramidal (TBP) geometry. A careful analysis of the equilibrium reported[17] in Scheme 2.5 reveals that the coordination at these sulfonyl phosphoranes **2** having a square pyramidal distortion on the pathway toward an octahedron, it is also accompanied by a change in the ring orientation. When no coordination is present, the eight-member ring occupies a diequatorial orientation, as seen in phosphorane **1**, **2** (Scheme 2.5).[18] However, it changes to an axial-equatorial orientation before distorting toward the SP geometry.



Scheme 2.5 Equilibrium from pentacoordination to hexacoordination.[17]

Other studies carried out by Ramirez[19] and others, suggested that hexacoordinated phosphorus compounds are formed during nucleophilic displacement reactions on pentacoordinated phosphorus compounds. Most of these studies have centered on oxyphosphoranes. In addition, there are studies of reactions of tetracoordinate phosphorus which have been considered to involve hexacoordinate states.[14,20] For example, nucleophilic catalysis of the phosphorylation of alcohols by the cyclic phosphate **3** in the presence of imidazole was proposed by Ramirez et al.[20] to proceed with ring opening via the hexacoordinate intermediate **A** to give **4** (Scheme 2.6). The imidazole catalyst acts in a nucleophilic assisted attack at phosphorus by the alcohol. Ramirez and co-workers[20] infer that analogous mechanisms may be important to the behaviour of some enzymes that are involved with phosphoryl group transfer whereby amino acid residues enter into the catalytic activity. The intervention of both five- and six-coordinate species is suggested.[14b,21]



Scheme 2.6 Nucleophilic catalysis of the phosphorylation of alcohols by the cyclic phosphate **3** in the presence of imidazole.

2.5 References

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Chapter 3

PHOSPHORUS-31 NMR SPECTROSCOPY

The phosphorus atom frequently plays a central role in the chemistry of most compounds in which it is incorporated. Without ^{31}P NMR spectroscopy, the task of sorting out the incredible changes in coordination number, and the additional stereochemical changes associated with the three-, four, five- and six- coordinate compounds world have been much slower.[1,2]

Chemical shifts in the nuclear magnetic resonance of ^{31}P were discovered by Knight.[3] Subsequent measurements, particularly those by Gutowsky and his co-workers[4] indicate that NMR spectroscopy can became a valuable tool for chemical studies involving phosphorus compounds. Today this technique can also be used to determine the complexity of a reaction mixture or the purity of products, because different signals are almost always seen for each phosphorus compound. Many other applications of phosphorus NMR have been made, such as performing conformational analysis and studying reaction mechanisms by means of signals for intermediates.

The large use of ^{31}P NMR is due to the presence of only one natural isotope with mass 31, so strong signals can be obtained with a small quantity of compound, that render the taking of phosphorus NMR spectra easy.[2]

3.1 Chemical Shifts

Phosphorus-31 chemical shifts have been observed over a range exceeding 1000 ppm. However, many classes of phosphorus compounds give signals within quite small parts of this range. The relationship between structure and phosphorus chemical shift is often well enough established to permit quite detailed structural inferences, even to the extent of identifying the stereochemistry in some instances. The presence of a lone pair of electrons on phosphorus tends to widen the chemical shift range, and additional information is usually required to obtain structural information. For organophosphorus compounds ^{1}H and ^{13}C NMR data can often be linked directly to the ^{31}P information. Together they form a very powerful structural tool for the chemist. Phosphorus-31

chemical shifts are reported relative to the signal for 85% phosphoric acid.[5] The acid is invariably used as an external reference due to its reactivity. Care must be taken when collecting data from the literature to establish whether the phosphorus isotope signal appears upfield or downfield of the standard, 85% phosphoric acid. There was a change in sign convention in the mid-1970s, and now positive chemical shifts are downfield of the standard.[2a]

Even if the ^{31}P NMR shifts extent in a large range, the vast majority are included in the region of about δ -200 to +300 ppm. Each type of functional group ha sits own range of shifts within this region. It should be noted that there is overlap of this functional group subregions, and it is not often possible to use only the ^{31}P shift, without other characterization for identify unambiguously a compound. Many factors have been considered to be important in effecting the shift for a particular structure. A few of this factor are reported to follow:[2b,6]

- Electron withdrawal by electronegative groups, generally considered to act by contracting the p-orbitals at P and causing deshielding.
- Resonance interactions at phosphorus with unsaturated groups that change electron density on phosphorus in either direction causing shielding.
- Chain lengthening and branching effects, which cause deshielding as the number of β-carbons to P increases or shielding as the number of γ-carbons increases.
- Changes in bond angles at phosphorus, increases in which are said to cause deshielding of 3-coordinate phosphorus and shielding in phosphates.
- Steric interaction in acyclic compounds manifested by shielding.

- Five cyclic-member compounds showed to be more deshield than the analogous six cyclic-member. This phenomena is caused by major overlapping between dπ-pπ orbital in the five cyclic-member compounds in which the bong angle is closer to 90°.

Besides structural properties can be achieved by analysis of ^{31}P NMR spectra. In fact each P-coordinations has its range of chemical shift that covered all the ordinary range (Figure 3.1). It could be important to note that 6-coordinate compounds are also found outside their usual range; in fact they can have a positive chemical shift, as reported in the literature.[7]

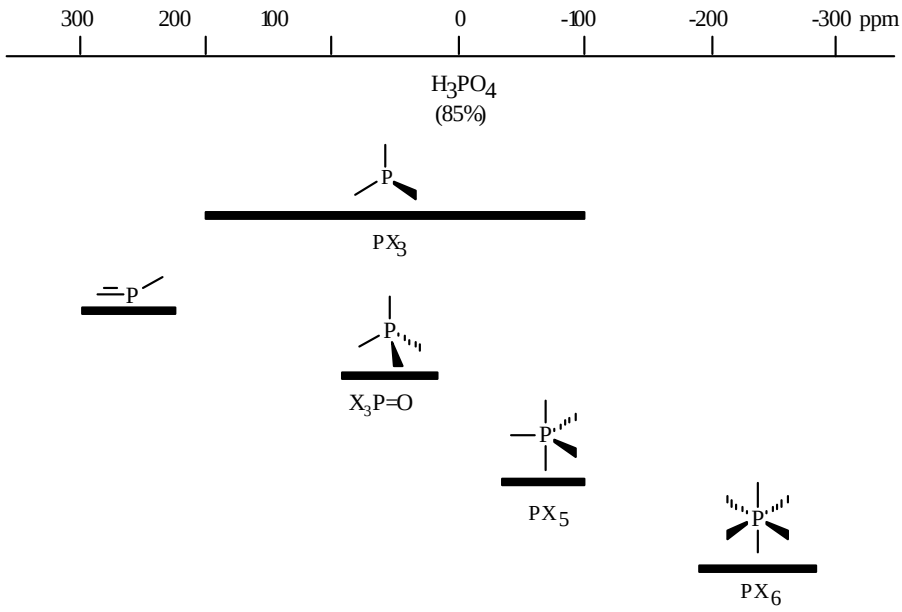

Figure 3.1 Chemical shift range for the different P-coordination.

3.2 Spin-Spin Coupling Constants

The ^{31}P nucleus coupled with ^{1}H, and both types of spectra show the effect. Couplings constants can be as small as a few Hertz or as a many as several hundred Hertz for the direct P-H bond. Because the coupling effect is commonly seen on ^{1}H spectra, but usually avoided by decoupling in ^{31}P NMR, coupling constants are usually determined from the previous spectra. Therefore couplings to neighboring protons are very useful for determining the nature and the number of aliphatic groups bound to the phosphorus atom. The protons of aryl groups rarely produce resolvable couplings in the ^{31}P spectrum.[2c]

The lone pair effect is clearly seen in the decrease of the positive $^{1}J(^{31}P,^{1}H)$ values from PH_4^+ (546-548 Hz) to PH_3 (182-195 Hz) to PH_2^- (138-140 Hz).[8] Although there is a general increase in $^{1}J(^{31}P,^{1}H)$ with increasing oxidation states of phosphorus, the ranges for the various oxidation states overlap considerably, perhaps owing in large measure to the reduction of s character in the P-H bond as the coordination numbers increase. As expected, the loss of a P lone pair upon coordination of a phosphine to a boron Lewis acid or a transition metal results in a marked increment in coupling. The effect of electronegativity is evident in the rise of $^{1}J(^{31}P,^{1}H)$ especially when electron electronegative halogens are bound to phosphorus.[9]

A different situation prevails for the coupling of ^{31}P with ^{13}C where useful couplings to phosphorus are manifest in proton decoupled ^{13}C NMR spectra. In this case the effect is seen only on the ^{13}C

NMR spectra, because the low natural abundance of ^{13}C (1.1%) in insufficient to lead to an observable number of coupled ^{31}P nuclei. Such couplings greatly aid the identification of the carbon resonances adjacent to phosphorus as well as providing important stereochemical information in many instances.[2c]

3.2.1 ^{31}P-^{11}B coupling

The one-bond coupling of ^{31}P and ^{11}B has been recorded mainly for tricovalent P ligands bonded to a BZ_3 moiety for which the range of couplings is 13-174 Hz. Most of these ^{11}B signals appear as a quartet due to the ^{31}P-^{11}B coupling. ^{1}N NMR spectra usually display a quartet (^{1}H-^{11}B coupling) which is further split into a doublet by ^{1}H-^{31}P coupling.[2c,10]

The difference between the chemical shift of the free tricoodinated phosphorus compound and the chemical shift of its borane adduct is called the coordination chemical shift (CCS), which varies depending on the nature of the groups bonded to phosphorus. Several compounds have been compared, and it appear that trialkyl- or triarylphosphines complexation with borane results in a rather strong deshielding (CCS = 95 to 133 ppm).[11]

3.3 References

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Part 2

ABIOTIC CHEMISTRY

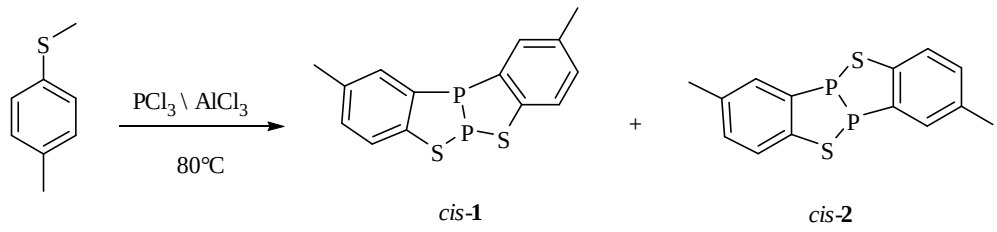
With the term “abiotic chemistry” we mean all reactions of the classical chemistry laboratory, in which the reactions are carried out in organic solvent, with all kind of molecules, and with conditions often very hard, without the intervention of any biomolecules.

Chapter 4

THE PHOSPHORUS DONOR REAGENT

4.1 General

During studies on the reactivity and use of PCl_3 in organic synthesis, Baccolini and his co-workers found[1] the surprising result that fused benzo-l,2,3-thiadiphospholes (**1**) was formed by reaction of p-methylthioanisole with PCl_3 and $AlCl_3$. This synthetic procedure has been improved during recent years and now it is possible to obtain compound **1** with good yields (45%), using a one-pot three-step procedure.[2] The prevalent product isolated from the reaction was the compound *cis*-**1**, and only in trace the isomeric compound *cis*-**2** (scheme 4.1). No appreciable amount of the corresponding *trans* isomers were observed.



Scheme 4.1 Synthesis of compound **1** (containing traces of **2**).

The X-ray crystal structure determination of *cis*-**1**[1] and *cis*-**2**[3] compounds showed that both of the molecules exhibit a 'butterfly' arrangement with the phosphorus electron lone pairs in an eclipsed conformation (Figure 4.1). As this conformation is unusual for a molecule containing a P(III)-P(III) single bond, a solid state ^{31}P-NMR study was performed. The changes in $^{1}J(P,P)$ and $\delta^{31}P$ observed from solution to solid state indicated that crystal packing effects force of two “wings” of the butterfly molecule to open slightly in the solid state.[4]

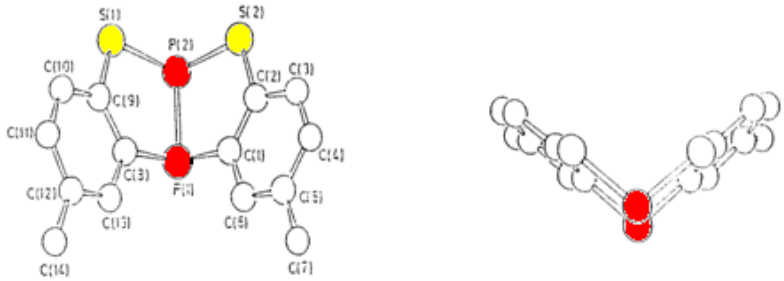
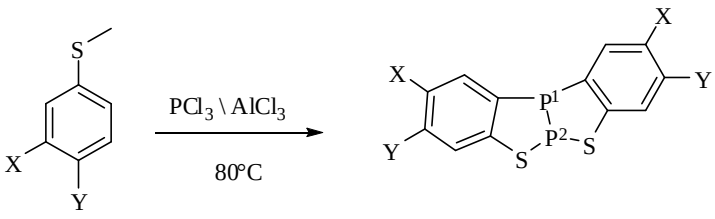


Figure 4.1 X-ray crystal structure of *cis*-**1**[1], where yellow indicates sulfur atoms and red indicates phosphorus atoms.

This method has also been generalized employing several alkyl aryl sulphides, providing in this way the corresponding fused benzo-l,2,3-thiadiphospholes, such as *cis*-**1**, but with a decrement of the obtained product.[5] In particular the tioanisoles (**3**) and PCl_3 and $AlCl_3$ were allowed to reflux in the absence of solvent for *ca*. 2h. and the products were purified by filtration on Florisil column. In the scheme 4.2 reports the products (**4**) are obtained by reaction of different alkyl- substituted tioanisoles (**3**) with PCl_3 and $AlCl_3$. The best results were obtained using a ratio (**3**)- PCl_3- $AlCl_3$ of 1:3:0.75. The yields of products (**3**) were also dependent on the starting sulphide. The substrate **3b** provided the higher yield. Compounds **4** were stable to air and moisture and for this reason easy to purify. The reaction appeared to be favoured when the methyl group occupied the *para*-position, presumably reducing the by-products arising from the electrophilic substitution of PCl_3 in that position. In addition the *ortho*-substituent does not allow the formation of **4** probably because of the steric hindrance of the methyl group.[5]



3 **4**

	X	Y	Yield%
a:	H	H	22
b:	Me	H	38
c:	H	Me	20
d:	Me	Me	35
e:	Et	H	30
f:	^{t}Bu	H	11

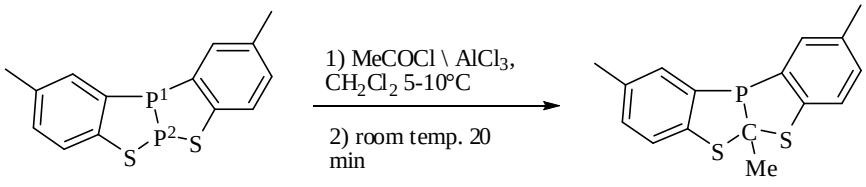
Scheme 4.2 Generalization of the method.

Exploiting the reactivity of the heterocycle **1** in order to synthesize other phosphorus and sulphur heterocycles, different reactions were carried out.[6,7]

This new system showed to be highly unstable in the conditions under which phosphines normally react, i.e. formation of phosphonium salts with alkyl halides, oxidation with H_2O_2 reaction with diethyl azodicarboxylate (DEAD)[8] /catechol or with phenyl azide. In such cases, rather than the

corresponding salts, oxides, spiro derivatives or phosphazenes[9] of **1**, decomposition products were obtained, presumably deriving from P-S and P-P bond cleavage.

Studying this instability of **1**, a Friedel-Crafts acylation with acetyl chloride and $AlCl_3$[6] was carried out and surprisingly, a highly stereospecific replacement of the phosphorus P^2 with the carbonyl carbon atom of acetyl chloride was obtained. This phosphorus-carbon exchange occurred under mild conditions in a one-pot reaction, and gave the cis-6-R-[1,3]benzothiaphospholo[2,3-b][l ,3]benzothiaphosphole derivative **5** in very good yields (scheme 4.3).



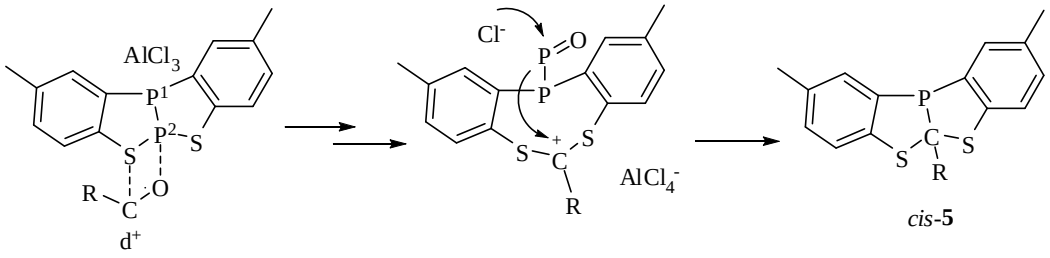
cis-**1** *cis*-**5**

Scheme 4.3 Exchange of P^2 by the carbonyl carbon atom of acetyl chloride.

A possible generalization of the reaction with other acyl chlorides was tried in order to obtain information about the mechanism involved in this phosphorus-carbon exchange.[6b] In all the reactions performed, the corresponding compound

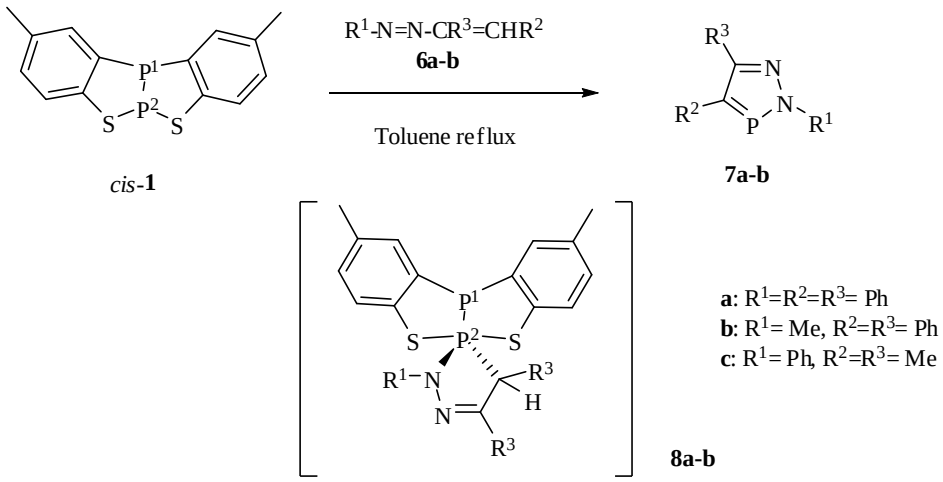
5-like were isolated in very good yields. In contrast, when acyl chlorides with R = ^{t}Bu, Ph, *p*-ClC_6H_4, CCl_3 were used, the starting material **1** disappeared to give formation of unidentified products. Only traces of the corresponding fused l,3-benzothiaphospholes were detected by GC-MS analysis. From these simple results it was possible to deduce that this exchange reaction was dependent on the steric factors associated with the acyl chloride. In fact, with a more forced R group, it was very likely that the cleavage of P-S and/or P-P bonds did occur, but the ring closure is disfavoured presumably because of steric congestion.

In scheme 4.4 a mechanism[6b] for the reactions is illustrated; it is based on the lability of the P-S bond, the affinity of the phosphorus for the oxygen atom, and the observed stereospecificity with inversion of configuration in the initial reaction. As depicted, it was supposed that initially a concerted breaking of the P-S bonds occurs with formation of C-S and P-O bonds; in the final step there is a ring closure, which is favoured when the R group is relatively small; this is in accord with the above experimental data.



Scheme 4.4 Proposed mechanism of the phosphorus-carbon exchange.

With the intention of continuing to explore the peculiar reactivity of compound **1**, the reaction with conjugated azoalkenes was investigated.[7] They are known to react with phosphorus halides[10] and phosphates,[11] but not with trisubstituted phosphines. Unexpectedly, all the isomers of phenylazostilbene **6a** reacted with **1** to afford the previously unknown diazaphosphole **7a**, and this procedure represents a new route for obtaining diazaphosphole derivatives (scheme 4.5). Unfortunately, all attempts to obtain or to characterize an intermediate adduct were unsuccesful. However, it is possible to hypothesise a spirocyclic adduct **8** with pentacoordinate P^2 atom, in probable equilibrium with different ionic forms. Its decomposition gave **7a-c**, presumably by a reductive elimination[12] mechanism. Unfortunately, it was not possible to identify other by-products in order to confirm the above hypothesis.



Scheme 4.5 Reaction with conjugated azoalkenes.[7]

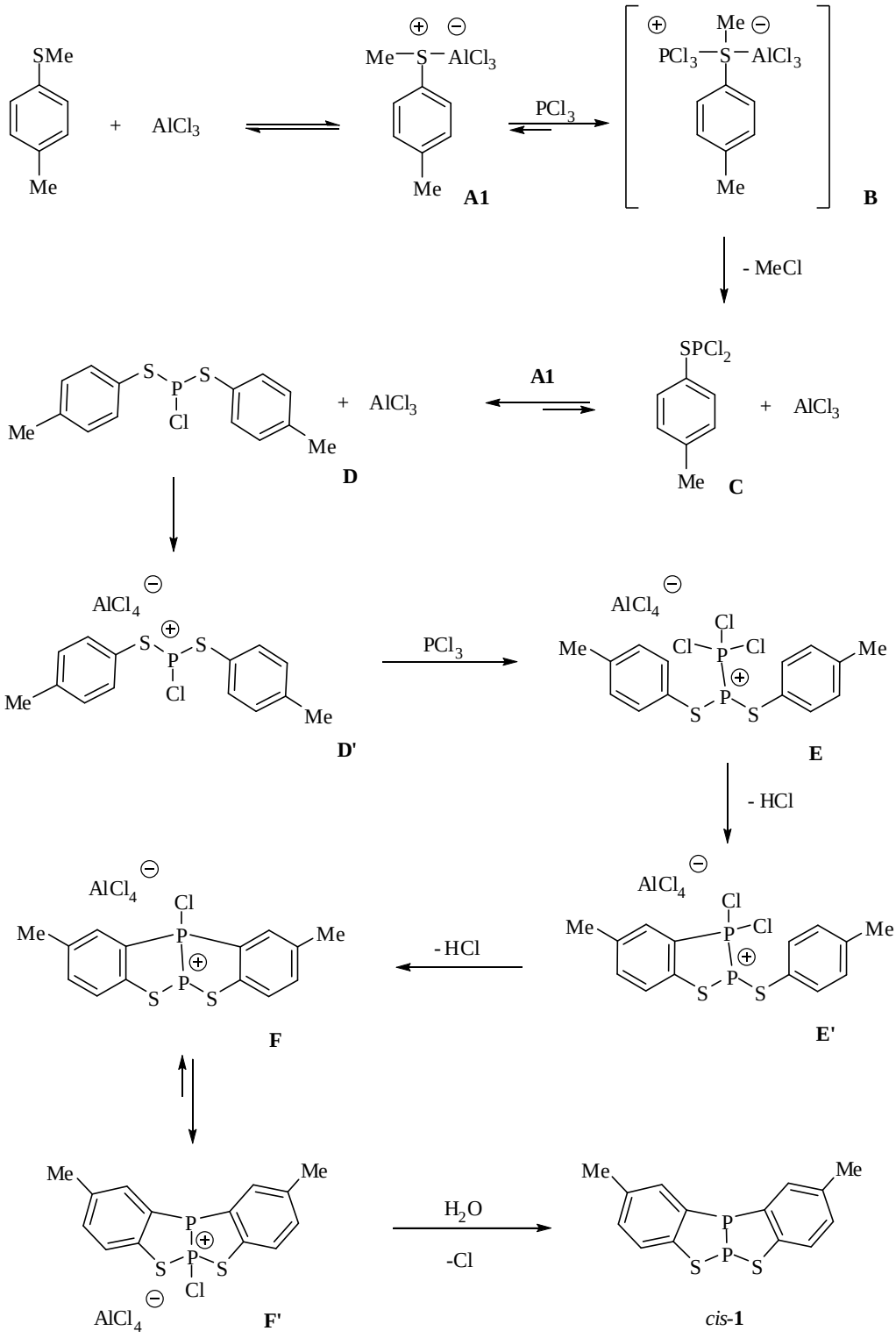
Since the formation of this heterocycle, the fused benzo-l,2,3-thiadiphosphole (**1**) from the reaction of *p*-methyl tioanisole, PCl_3 and $AlCl_3$ resulted unusual, its formation mechanism has been studied.[13] The principal problem was the complexity of the cyclization reaction, but fortunately the separation and the characterization of the prevalent product (*cis*-**1**) was very easy.

The breaking of two S-Me bonds, the formation of two C-P bonds, two P-S bonds, and one P-P bond are involved in this cyclization, and several pathways could be hypothesised, but due to a lack of data it had not been possible to determine an unequivocal reaction pathway. In order to determine the most probable pathway, it was necessary to uncover some information regarding the demethylation process, the *ortho*- and S-phosphorylation, the P-P linkage formation and, if it was possible, to have some explanation for the facile regioselective and stereoselective formation of *cis*-**1**.

It is well documented in the literature[14] that when a diphenyl sulfide is caused to react with $AlCl_3$, a sulfonium salt or complex is formed in a reversible manner, and evidence for methyl phenyl sulfide-$AlCl_3$ complex formation has also been reported.[15] In addition, when this complex is treated with other reagents, a cleavage of the C-S bond occurs presumably via a tetracovalent sulfur compound.[14-16] Furthermore, benzyl phenyl sulfide is known[16] to form a complex with $AlCl_3$, which undergoes reaction with water to give thiophenol and benzyl chloride.

In consideration of the above-mentioned observations reported in the literature, a multi-step mechanism was proposed as depicted in Scheme 4.6.

In order to obtain supporting evidence for the above-proposed multistep mechanism, a series of reactions using various conditions were conducted (different reagent ratios and various temperatures). Aliquots of the reaction mixtures were analyzed by ^{31}P- and ^{1}H-NMR spectroscopy and by GC-MS determinations.[13] The ^{31}P chemical shifts and P-P and P-H coupling constants found,[13] were in good agreement with the formulation of intermediates reported in the Scheme 4.6.

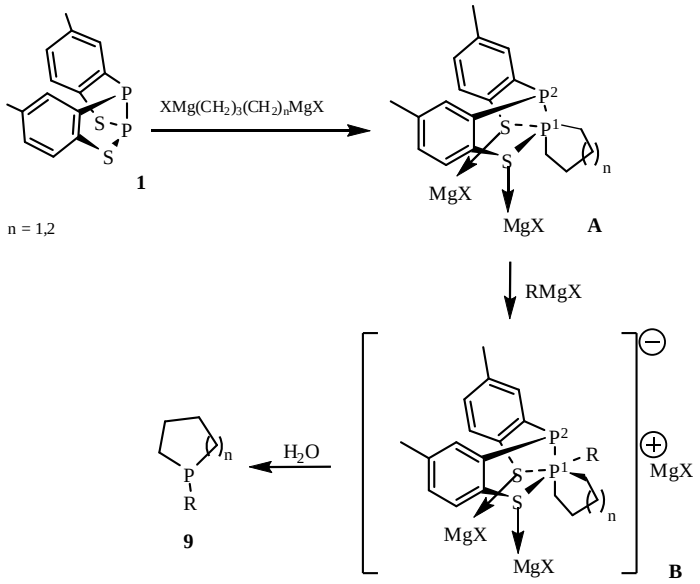


Scheme 4.6 Proposed mechanism of formation of fused benzo-l,2,3-thiadiphospholes (*cis*-**1**).[13]

After the mechanism study, an improved synthetic procedure was formulated, and now, as reported above, it is possible to obtain the compound *cis*-**1** in moderate yields.

The increment in the yield has permitted the development of the studies on the reactivity of this new heterocycle. As reported above, in both reactions[6,7] carried out on the compound **1**, the molecule reacted losing a phosphorus atom P^2.

Its reactivity was also studied using Grignard reagents, demonstrating that compound **1** could react with those reagents in an unusual manner. In particular the simultaneous addition of an equimolar mixture of a bis-Grignard (*n* = 1, 2) and a mono-Grignard RMgBr to an equimolar amount of **1** at room temperature, which gave the cyclic tertiary phosphines **9** as the prevalent product after quenching with water.[17]

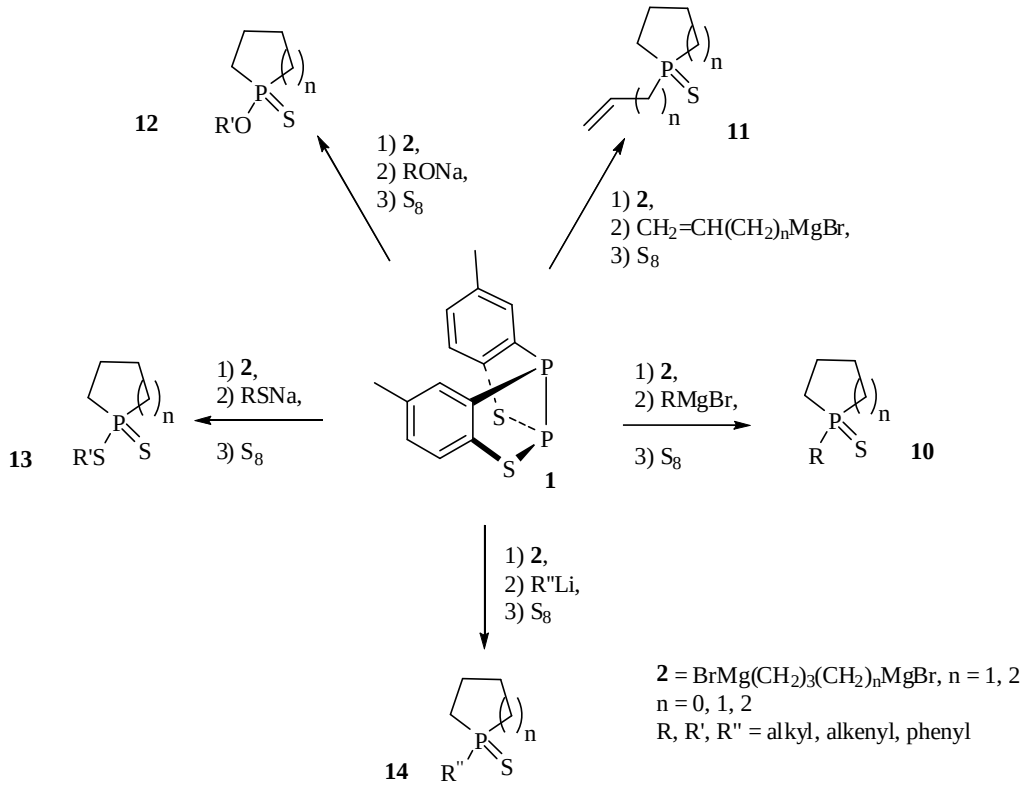


Scheme 4.7 Reaction between reagent **1** and bis- and mono-Grignard reagents.

These results were explained by the presumed intervention of hypervalent phosphorus intermediates penta- and hexacoordinates such as **A** and **B,** in which the dibenzo-butterfly moiety of reagent **1** might favour their formation. This observed favoured cyclization might be in accord with a hypervalent intermediate in which the formation of a cyclic form is favoured by a larger factor (10^5–10^8) with respect to an acyclic form (as reported in the Chapter 2). With the aim of obtaining information about the stability of the hypothetical intermediate **A**, the reaction was carried out in a three-step procedure between bis-Grignard reagents and **1** monitoring the progress of the reaction by ^{31}P NMR spectroscopy.[18] A few minutes after mixing the reagents the disappearance of the two doublets of **1** was noted [δ = 88.3 (d, P^1), 65.4 (dt, P^2, ^3JPH = 7.8 Hz), ^1JPP = 211.5 Hz] and the concomitant appearance of two new doublets [δ = -43.3 (dm, P^1, *J*PP = 188 Hz); δ = -47.0 (dt, P^2 *J*PH = 7 Hz), *J*PP = 188 Hz)], tentatively assigned to the intermediate **A** (Scheme 4.7). The large P-P coupling constant indicates that intermediate **A** has a P-P bond again; the doublet of triplets observed for P^2 indicates that this P atom is bonded to two phenyl groups, while the doublet of multiplets

suggests that P^1 is bonded to alkyl groups. This intermediate **A** is very stable. Only after the addition of a mono-Grignard reagent and quenching with water, the disappearance of these signals and the appearance of new signals corresponding to the phosphine **9** were observed.[18] After the study on the reaction mechanism, the reaction was carried out in a one-pot, two-step procedure, where the addition in two steps of equimolar amounts of a bis-Grignard reagent and a mono-Grignard reagent RMgBr to one equivalent of **1** at room temperature, gave the cyclic phosphine **9**, after quenching with water. In this manner the yield was improved, with a better control of the final products (Scheme 4.7).

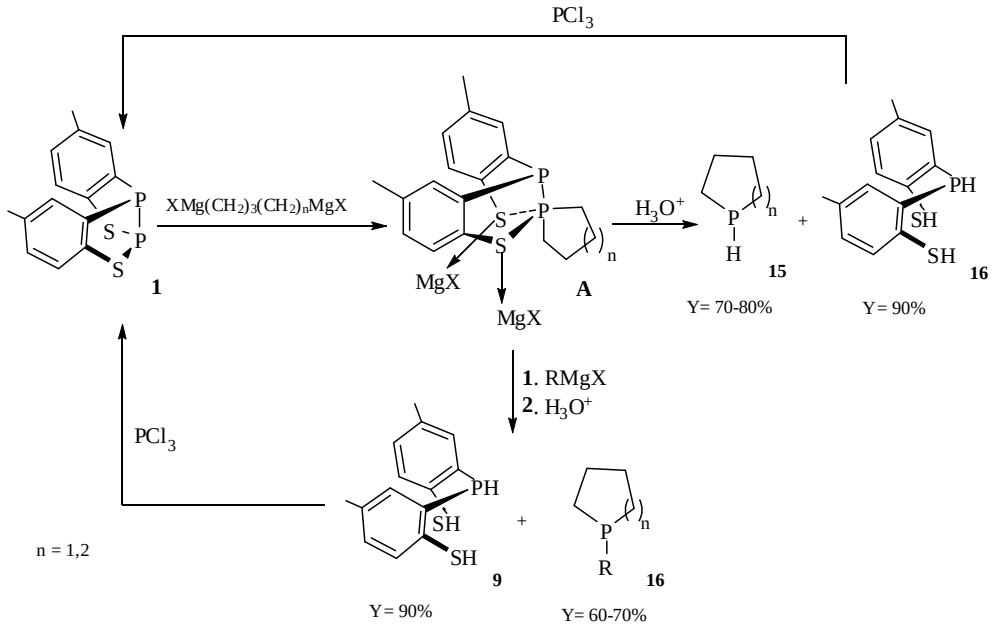
With similar methods different classes of tertiary cyclic phosphines were obtained (see Scheme 4.8). In order to easily characterize the compounds, the final reaction mixture was treated *in situ* with elementar sulfur to obtain the corresponding cyclic phosphines sulfides **10**, **11**.[17, 18] If the reaction mixture is treated with water instead of S_8 the corresponding cyclic phosphines **9** are obtained. Consequently, it was discovered in the second step that a large variety of Grignard reagents and other nucleophilic reagents, such as sodium alcoholate or thiolate and lithium derivatives could be used, obtaining various 1-substitued cyclophosphine derivatives **12**, **13** and **14** respectively (Scheme 4.8).[19]



Scheme 4.8 Reaction of compound **1** with bis-Grignard reagents and mono-Grignard reagents (containing alkyl, phenyl and alkenyl groups), R'ONa, R'SNa and lithium derivatives.

The above reaction was further studied when intermediate **A**, formed by reaction of **1** with one equivalent of bis-Grignard reagent, was treated with water. Unexpectedly, in this case, secondary

cyclic phosphanes **15**[20] were obtained in 70–80% yields (Scheme 4.9).[21] Moreover, if the reaction mixture was treated with acidic water instead of only water, the new compound **16**, which is the end product derived from **1**, was isolated, in very good yields (before it could only be observed by a GC-MS in the reaction mixture). These can be easily separated by treating the solution with aqueous basic solution; in this way the sodium salt of **16** dissolves in the aqueous soluton, whereas the organic phase contains almost pure cyclic secondary phosphines, which can be purified by distillation. Compound **16** can be recovered from the basic aqueous layer by acidification and extraction, and purified by distillation. Simply treating a dry solution of **16** with an equimolar amount of PCl_3 regenerates **1** in sufficiently pure form that it can be reused without further purification.[20]



Scheme 4.9 Synthesis of secondary and tertiary cyclic phosphines, with recycling of starting reagent **1**.

Following on from the results obtained with secondary phosphines **15**, the reaction to obtain tertiary cyclic phosphines **9** was carried out using the same treatment of the crude reaction mixture used to obtain secondary cyclic phosphines, and also in this case the by-product **16** was isolated.

Due to the simple isolation of **16** and its easy recycling into **1**, these syntheses can be considered atom-economic.

4.2 One pot three-steps procedure for reagent fused benzo-1,2,3-thiadiphosphole

The reaction was conducted in a 150 mL three-necked flask equipped with a condenser, a dropping funnel, and with inlet for dry N_2. A mixture of *p*-methylthioanisole (0.04 mol) and $AlCl_3$ (0.03 mol) was stirred under N_2 for about 10 minutes (until the $AlCl_3$ was completed soluble) during which the colour changed to yellow-pink. Then PCl_3 (0.04 mol) was added, and the resulting red-brown solution stirred for 10 minutes. After that other PCl_3 (0.012 mol) was added, the N_2 flow stopped and the mixture heated to reflux (90-100°C) for 6-8 hours.

The reaction was monitored using GC-MS. When the reaction was finished the solution was cooled down to 0°C and CH_2Cl_2 (30 mL) was added. The resulting solution was treated under stirring with water. Extraction with CH_2Cl_2 (30 mL) and subsequent crystallization of the crude product from CH_2Cl_2-Et_2O gave pure reagent **1**.

40-60%; White crystals; m.p. = 157-159°C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.41 (d, 2H, J_{PH} = 8.0 Hz), 7.25 (d, 2H, $^1J_{HH}$ = 7.5 Hz), 6.98 (d, 2H, $^1J_{HH}$ = 7.5 Hz), 2.28 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$ 75.46): 141.6, 139.96 (d, J_{PC} = 29.6 Hz), 135.5 (d, J_{PC} = 7.4 Hz), 131.7 (d, J_{PC} = 27.7 Hz), 130.5, 124.9, 20.8; ^{31}P NMR (121.47 MHz, $CDCl_3$, ext. 85% H_3PO_4): 65.4 (d, J_{PP} 211.5 Hz), 88.3 (d, J_{PP} 211.5 Hz); GC-MS (m/z, %): 243 (M^+), 211, 153, 121, 77, 63; HRMS (EI) calcd for $C_{14}H_{12}P_2S_2$: 305.9855, found: 305.9859.[1]

2,10-dimethyl[1,2,3]benzothiadiphospholo[2,3-b][1,2,3]benzothiadiphosphole 12-oxide (1') : ^{31}P NMR (161.90 MHz, $CDCl_3$, ext. 85% H_3PO_4): 20.0 (d, J_{PP} 256.6 Hz), 100.9 (d, J_{PP} 256.6 Hz).

4.3 References

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Chapter 5

ROLE OF THE PHOSPHORUS:

CATALYTIC TRANSPORT SYSTEM OF ELEMENTS, SYNTHESIS OF ARSINE, STIBINE AND BISMUTHINE DERIVATIVES[1]

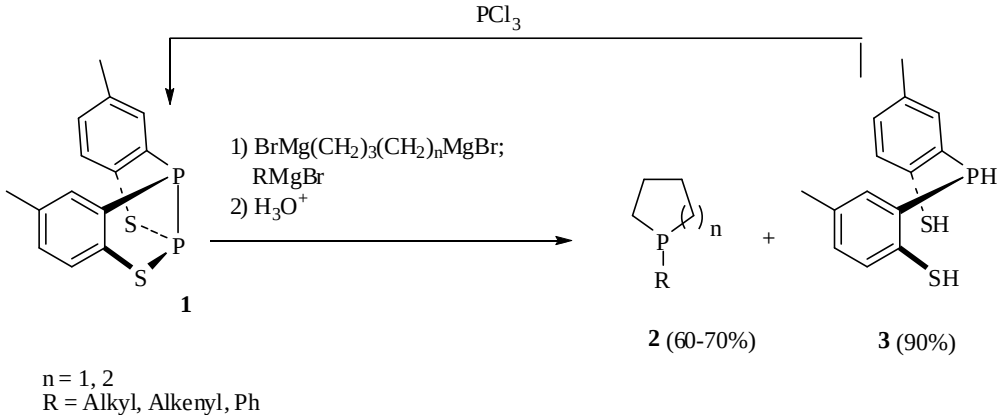
5.1 Introduction

The heterocyclic chemistry of arsenic, antimony and bismuth has its roots in medicinal chemistry of the early 1900s. With the discovery that an organoarsenic compound provided a cure for syphilis, many new arsenic compounds were prepared and tested for their potential medicinal properties. Interest in organoantimony compounds arose only after the chemotherapeutical properties of organoarsenic were discovered.[2]

Organoarsenic and organoantimony have received much less attention than the analogous organophosphorus compounds in past years. Only recently these compounds have been revaluated for their coordination properties and application as ligands in coordination chemistry.[3] Unfortunately the number of available syntheses is low and often required multi-step reactions.[4]

5.2 Results and discussion

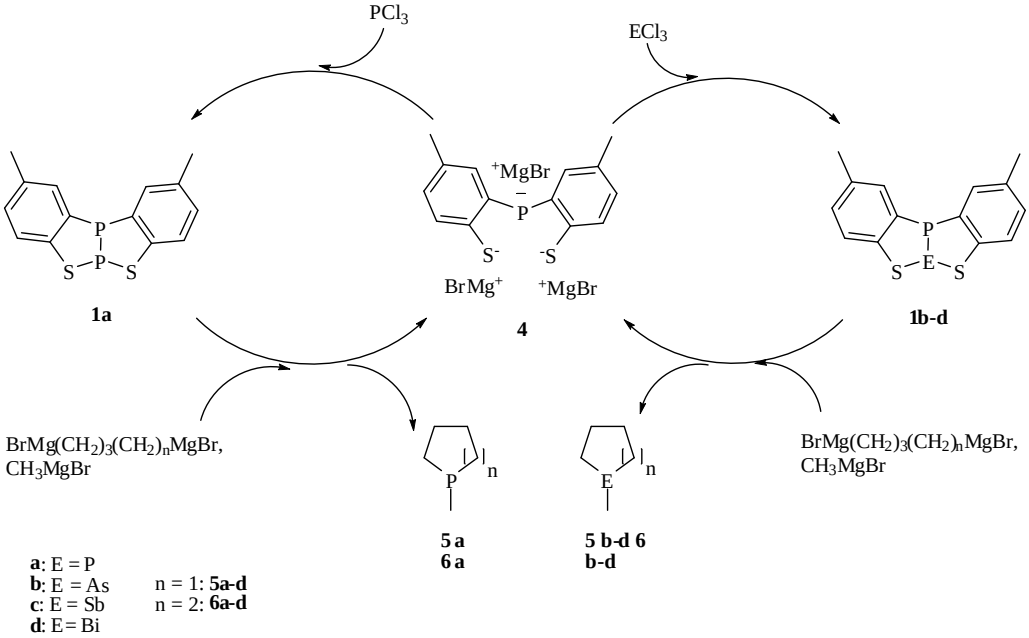
In previous studies it was reported[5] that the formation of cyclic tertiary phosphines such as **2** is achieved in very high yields and in a one-pot reaction by simultaneous addition of a bis-Grignard and a mono-Grignard reagent to the reagent **1a** (Chapter 4). Treatment of the resulting reaction mixture with aqueous acid gave cyclic phosphines **2** and the end product **3**, which is the residue of **1a**. Treatment of **3** with PCl_3 quantitatively and immediately regenerates the starting reagent **1a** (Scheme 5.1).



Scheme 5.1 **Synthesis of cyclic tertiary phosphines with recycling of reagent** 1**.**

Additional studies on the above reported reaction, showed that this reaction could be considered an unusual 'transport' system of elements (Scheme 5.2) formed by two molecules. The first is a benzothiadiphosphole derivative (**1a**), the phosphorus donor reagent that can react with different Grignard reagents. In the case of the simultaneous addition of an equimolar amount of bis- and a mono-Grignard reagent to 1a, cyclic tertiary phosphines (**5**, **6a**) are easily obtained.

The second is the by-product **4** that is the residue of the reagent 1a obtained after expulsion of the phosphorus atom, when tertiary phosphines (**5a**, **6a**) are produced in a 70-80% yield.

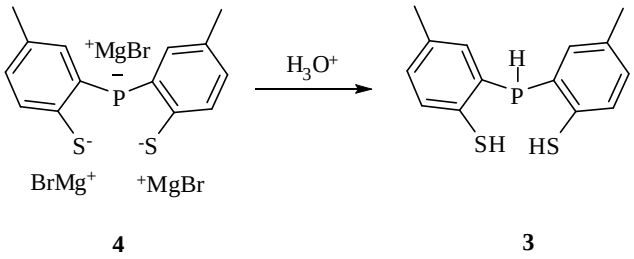


Scheme 5.2 **Catalytic cycle using the catalyst** 4.

The compound 4 is the magnesium salt of **3**, that in previous reactions was recovered as the analogous acid derivatives **3** (Scheme 5.3). This compound **4** is easily retransformed into the starting reagent **1** by simple addition of PCl_3. When the addition of PCl_3 is done directly into the reaction mixture, after formation of phosphines, the starting reagent 1a is directly regenerated without previous separation of the salt **4**. In this way the reagent 1a can react again with the bis- and mono-Grignard reagents producing phosphines **5a**, **6a** and the by-product **4**. Therefore it is possible to repeat this transport process of the P atom theoretically an infinite number of times.

The only limitation to the number of cycles is due to the quantity of starting material. In fact in every cycle 90% of initial 1a is obtained, this means that after some cycles the quantity of **1a** is low (in respect to the other components of reaction mixture) and measuring out the amount of Grignard reagents to add is very difficult.

It is important to note that the molecule **4** is the true carrier of the P element and might be considered a "catalyst" both, for its ability to obtain products which are quite difficult to synthesize by other methods, and for the fact that it can be completely recovered at the end of the process.



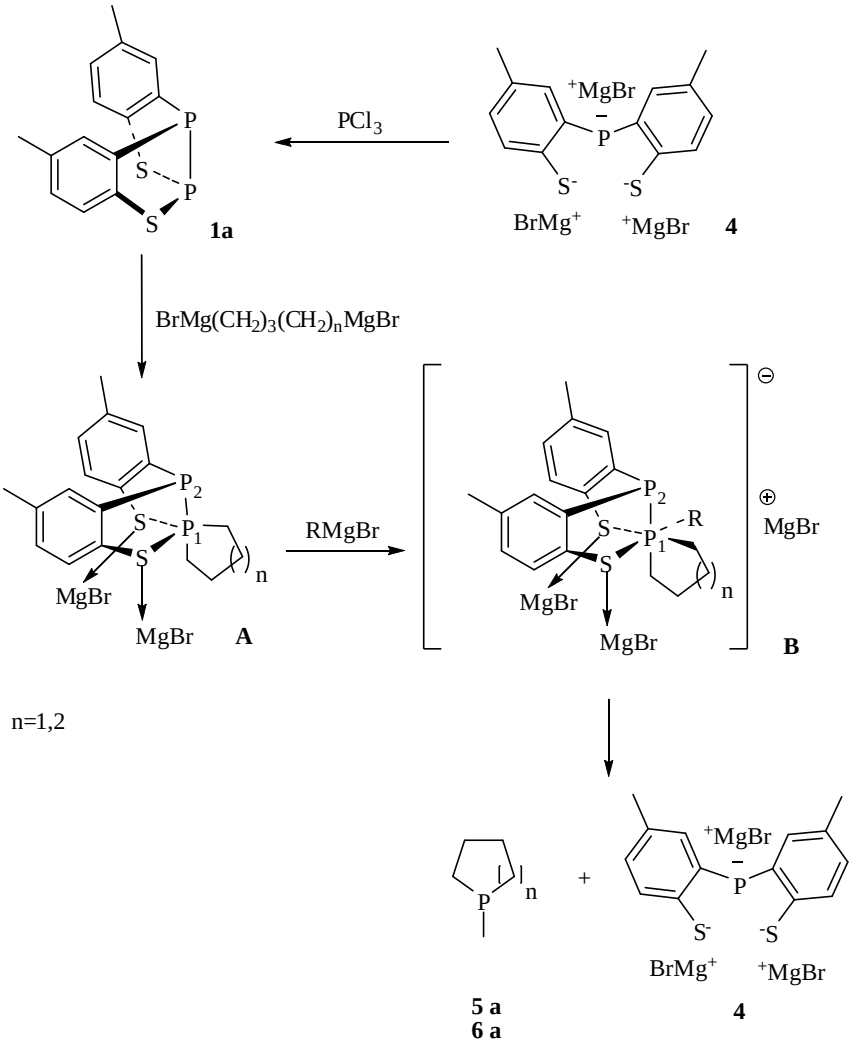
4 **3**

Scheme 5.3 Addition of H_3O^+ to compound **4** produces **3**

These results about phosphorus donation were explained[6] by the intervention of a pentacoordinate phosphorus intermediates such as **A,** which was also isolated and characterized by ^{31}P NMR, and a hexacoordinate species such as **B** very instable (Scheme 9.4) in which the folded "dibenzo-butterfly" moiety of reagent **1a**, greatly favours their formation.[7]

In fact, it is reported that in the hypervalent phosphorus species the presence of rings is a factor of enormous stability, reducing overcrowding.[7] For every cycle in a pentacoordinate species the stabilization is improved by a high factor (about 10^6- 10^8) in respect to the pentacoordinate species without the cycle. If an additional small ring is generated during the reaction, as in the case of bis-Grignard reagent, a further stabilization of these hypervalent intermediates is achieved. As a consequence, the reaction of bis-Grignard reagent that gives a new cycle around the phosphorus atom is highly preferred over the reaction of a mono-Grignard reagent in which there is not this cyclization. For this reason it is possible to carry out the reaction with the simultaneous addition of both bis- and

mono-Grignard reagents always obtaining the same product **5a** and **6a** in very high yields as occurs in the case of the subsequent addition of the two reagents.



Scheme 5.4 Mechanism of reaction.

The reaction between benzothiadiphosphole **1**, pentamethylenbis-(magnesium bromide) and methylmagnesium bromide was carried out in the NMR tube in THF and followed by ^{31}P NMR spectroscopy. After addition of one equivalent of bis-Grignard reagent respect to **1** only the presence of intermediates **A** [δ= -43.2 (d, *J*= 190 Hz), -46.7 (d, *J*= 190 Hz) ppm] was observed. Then after addition of a further equivalent of mono-Grignard reagent, the hexacoordinated intermediate **B** was observed in very low concentration (tentatively assigned [δ= 56.9 (d, *J*= 216 Hz), -56.8 (d, *J*= 216 Hz) ppm]). The spectrum of the reaction mixture after time showed presence of **6a** [*δ*= -41.7 ppm] and catalyst **4** [*δ*= -57.7 ppm].

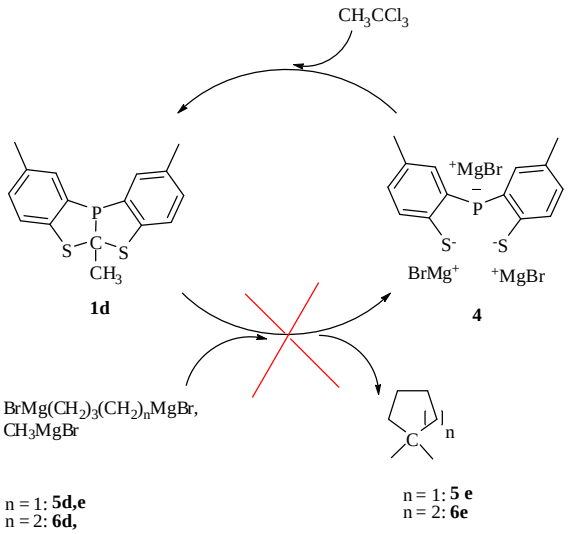
In addition, this process is highly favoured when organomagnesium derivatives are used, while it is highly disfavoured when zinc or lithium derivatives are used. The probable effect of Mg ions can be easily explained by imaging that the coordination of the magnesium atom to a sulfur atom would activate P^1 of intermediate **A** toward a further nucleophilic attack to give the instable hexacoordinate **B**. A further indication of the importance of the magnesium in this process lies in the fact that when

we carried out the reaction between **1a** and phenylzinc bromide, any phosphinic product such as **5a**, **6a** was recovered and the use of analogous lithium reagent gave only ring opened products of **1a**.

These findings, together with the possibility of easily transforming the residue **4** in the starting reagent **1a** by the simple addition of PCl_3 prompted us to use **4** to obtain similar transport processes with other elements in which the formation of hypervalent species is easy as in the case P element. These elements are As and Sb which have analogous atom electron configuration. In fact, by simple treatment of compound **4** with $AsCl_3$, $SbCl_3$ and $BiCl_3$, the arsenic-heterocycle 1b, the antimonium-heterocycle **1c** and the bismuth-heterocycle 1d were obtained. These heterocyclic compounds **1b-d**, as reported for **1a**, can be used as arsenic, antimonium and bismuth donor reagents for the synthesis of tertiary cyclic arsine **5b**, **6b** in 60-70% yield, tertiary cyclic stibine **5c**, **6c** in 50-55% yield and tertiary cyclic bismuthine **5d**, **6d** in 25-30% yield (but in this case compound 1d give also a dimmer insoluble product that inhibits the reaction) in a continuous cycle such as that depicted in Scheme 5.2. The reported mechanism in Scheme 9.4 can also be used to explain reaction in which As, Sb and Bi are involved and in general other elements which can have stable hypercoordinated species.

When the same process was carried out in order to obtain C derivative (treating catalyst **4** with CH_3CCl_3 for C) we obtained the corresponding intermediate **1e** (scheme 5.5) but the subsequent addition of bis- and mono-Grignard reagents did not generate the corresponding cyclic compounds **5e** and **6e**. This is in accord with the fact that in the case of C the hypervalent species, penta and hexacoordinated, are very unstable or impossible.

As follows the compound **4** can be compared with a catalyst, because it is used to catalyse different processes that cannot work without it and it is recovered at the end of the reaction. Instead the compounds **1a**,**b**,**c** could be seen as activated forms of the catalyst **4**.



Scheme 5.5 Carbon heterocyclic derivatives **1e**.

5.3 Experimental Section

5.3.1 General

NMR spectra were recorded at 300 (400) and 121.45 (161.9) MHz for ^{1}H and ^{31}P, respectively. Chemical shifts are referenced to solvent THF (^{1}H NMR, 1.8 ppm and ^{13}C NMR, 26.7 ppm), and external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. THF was distilled from sodium benzophenone ketyl. All Grignard reagents used, both commercially available and prepared from the corresponding alkyl halide and magnesium turnings, were titrated immediately prior to use by standard methods.[8] Air and moisture sensitive solutions and reagents were performed under dry argon atmosphere using standard Schlenk-type techniques. All solvents were purified appropriately before use and degassed immediately prior to use. Benzothiadiphosphole **1a** was synthesized as decribed (Appendix 1).[9] From reagent **1a** and catalyst **4**, compound **5** is obtained easily, as reported in Appendix 2.[10]

5.3.2 Isolation and characterization of compound 4

After reaction of reagent **1** with bis- and mono- Grignard reagent (see preparation of compounds **5**, **6**), and concentration of solution by vacuum pump (1/5 of the starting volume), the resulting suspension was filtered carefully under argon atmosphere. The white salt (**4**) was washed one time with 1-2 ml of anhydrous THF (the compound **4** is almost insoluble in THF, but reacts with traces of water to produce compound **3**). Compound **4** was conserved as suspension in anhydrous THF under argon (in this way it can be preserved for 2-3 days).

White solid; ^{1}H-NMR (400 MHz, THF d_8): δ = 7.42 (br s, 1H), 7.28 (br s, 1H), 7.05 (br s, *J* ~ 6.6 Hz, 1 H), 7.00 (br s, *J* ~ 6.6 Hz, 1 H), 6.54 (d, *J* = 6.8 Hz, 1 H), 6.48 (d, *J* ~ 6.8 Hz, 1 H), 2.20 (s, 3 H), 2.11 (s, 3 H); ^{13}C-NMR (100.56 MHz, THF d_8): δ = 146.8, 146.1, 143.0 (d, *J* = 28 Hz,), 141.9 (d, *J* = 30 Hz), 135.9 (d, *J* ~ 91 Hz,), 134.1 (d, *J* ~ 91 Hz,), 135.2, 134.6, 133.4, 129.7, 127.1, 126.0, 22.7, 22.6; ^{31}P-NMR (161.9 MHz, THF d_8) δ = -79.4 (m).

5.3.3 Preparation of new heterocycles 1b-1d

To a suspension of compound **4** (0.588g, 1.0 mmol) in THF (10 mL) under argon atmosphere, one equivalent of arsenic trichloride (or antimony trichloride or bismuth trichloride or 1,1,1-trichloroethane), in the case of the formation of compound **1b** (or **1c**, **1d**, **1e** respectively), was added (particular care must be taken in the manipulation of these reagents because of their toxicity). The solution turned immediately pale yellow (or pale green in the case of the formation of compound **1c** or orange in the case of formation of the compound **1d**). After 20 min. the solvent was removed giving quantitatively compound **1b** (or **1c**-**e**) which were immediately characterized and stored under argon atmosphere.

Compound **1c** and **1d** has to conserve in diluted solution of THF, because it easily forms a solid precipitate that is insoluble.

In the case of addition of CH_3CCl_3 to **4**, the reaction was very slow and the resulting yield in **1e** was very poor. As a consequence, the heterocycle **1e** was not isolated but only identified in the reaction mixture by GC-MS and ^{31}P NMR spectroscopy, with reference to the same compound synthesized via the procedure reported in Appendix 3. Also in the reaction with bis- and mono-Grignard reagents, the compound **1e** was synthesized using the procedure reported in Appendix 3.

2,10-dimethyl[1,3,2]benzothiaphospharsolo[2,3-*b*][1,3,2] benzothiaphospharsole (1b): ^{1}H NMR (400 MHz, THF-d_8, 25°C): δ (ppm)= 7.54 (d, *J*=9.5 Hz, 2H), 7.26 (d, *J*=8.2 Hz, 2H), 6.96 (d, *J*=8.10 Hz, 2H), 2.28 (s, 6H, CH_3); ^{13}C NMR (100.56 MHz, THF-d_8, 25°C): δ (ppm) = 145.3, 143.8 (d, *J*=33 Hz), 137.0 (d, *J*=9 Hz), 134.8 (d, *J*=30 Hz), 132.3, 127.6 (d, *J*=3 Hz), 22.2; ^{31}P NMR (161.9 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ (ppm)= 78.6 (br.s., line width ~15Hz); $\{^{1}H\}^{31}P$ NMR (161.9 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ (ppm)= 78.6 (t, J_{PH}=8.7 Hz); GC–MS: m/z (%): 350 (35) $[M]^+$, 243 (100), 107 (14); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{12}AsPS_2$, 349.9334; found, 349.9332.

2,10-dimethyl[1,3,2]benzothiaphosphastibolo[2,3- b][1,3,2] benzothiaphosphastibole (1c): ^{1}H NMR (400 MHz, THF-d_8, 25°C): δ (ppm)= 7.54 (d, *J*=10.3 Hz, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 6.84 (dm, *J*=8.0 Hz, 2H), 2.26 (s, 6H, CH_3); ^{13}C NMR (100.56 MHz, THF-d_8, 25°C): δ (ppm)= 147.6, 137.6 (d, *J*=31 Hz), 135.5 (d, *J*=10 Hz), 133.7 (d, *J*=69 Hz), 131.4, 130.7, 21.9; ^{31}P NMR (161.9 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ (ppm) =52.7 (br. s., line width ~42 Hz); GC–MS: m/z (%): 396 (23) $[M]^+$, 243 (100), 153 (6), 121 (12); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{12}PS_2Sb$, 395.9156; found, 395.9152.

2,10-dimethyl[1,3,2]benzothiaphosphabismolo[2,3-*b*][1,3,2] benzothiaphosphabismole (1d): ^{1}H NMR (400 MHz, THF-d_8, 25°C): δ (ppm)= 7.71 (d, *J*=14.0 Hz, 2H), 7.25–7.08 (m, 4H), 2.29 (s, 6H, CH_3); ^{31}P NMR (161.9 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ (ppm)=35.0(s, line width ~23 Hz); {^{1}H}^{31}P NMR (161.9 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ (ppm)=35.0 (t, J_{PH}=14.0 Hz). MS: m/z = 484 $[M]^+$, 275, 243, 211, 153, 121.

5.3.4 Preparation of compounds 2a–c and 3a–c by reaction between ECl3 and Grignard reagents in the presence of catalyst 5. General two-steps procedure

ECl_3 (2.0 mmol, E=P, As, Sb) was added, under an argon atmosphere and at room temperature, to a suspension containing catalyst **5** (2.0 mmol) in THF (20–30 mL). After about 20 min. the reaction mixture turned clear (uncoloured when E=P, pale yellow when E=As, pale green when E=Sb, and yellow-orange when E=Bi), so indicating that the formation of compound 1a–d occurred, as confirmed by 31P NMR spectroscopy of the reaction mixture. To the solution of 1, a solution containing $BrMg(CH_2)_nMgBr$ (*n*=1 or 2, 2.0 mmol) was added, at room temperature. After about 90 min. a solution of CH_3MgBr (2.0 mmol) in THF was slowly added dropwise. The reaction course was monitored by GC–MS and ^{31}P NMR spectroscopy: when the signals of starting reagent 1 disappeared, with concomitant appearance of those of **2** (or **3**) and of **5**, one equivalent amount of ECl_3 was added to the crude reaction mixture and the concomitant formation of corresponding reagent **1** was detected. The yield of this reaction is nearly quantitative, and the cycle can be repeated more times, thus allowing to a continuous increase in the yield of cyclic derivative. The only limitation to the number of cycles is due to the quantity of starting material. In fact, in every cycle 90% of initial **1** was obtained therefore after some cycles the quantity of **1** become low with respect to other components of the reaction mixture, and measuring out the amount of Grignard reagents to be added become very difficult. At the end of the process compound **5** can be recovered by filtration under argon and cyclic compound, present in the filtrate, can be purified, after removal of the reaction solvent, by distillation. Otherwise, the isolation of the reaction products can be obtained by partial evaporation of the solvent and treatment of the crude reaction mixture with degassed acidic (HCl) aqueous solution. Extraction with CH_2Cl_2 gives a mixture containing compound **2** (or **3**) and the residue **4**, that can be easily separated by treatment of the organic solution with degassed aqueous NaOH followed by extraction with CH_2Cl_2. The cyclic product, present in the organic layer, was immediately purified by removal of the solvent and purified by distillation. Compound **4** was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and purified by bulb-to-bulb distillation and stored under argon, as previously reported[4].

1-methylphospholane (5a): Colourless oil, bp 122–125°C (760 mmHg), Lit.:[11] 122–124°C (760 mmHg); 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.20–1.20 (m, 8 H), 1.28 (d, 3 H, *J* = 2.7 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$) δ (ppm) = –38.2 (m); GC-MS (m/z, %): 102 (85) HRMS (*m*/*z*): $[M]^+$ calcd for $C_5H_{11}P$, 102.0598; found, 102.0601; analysis (% calcd, % found for $C_5H_{11}P$): C (58.81, 58.79), H (10.86, 10.88).

1-methylarsolane (5b): Colourless oil, bp 66-69°C (15–18 mmHg), Lit.:[12] 65-66°C (15 mmHg); 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.75–1.25 (m, 8 H), 0.83 (s, 3 H); GC–MS (m/z, %): 146 (M^+, 100), 131 (39), 132 (23), 118 85, 103 (57), 90 (18), 55 (31).; HRMS (*m*/*z*): $[M]^+$ calcd for $C_5H_{11}As$, 146.0624; found, 146.0626; analysis (% calcd, % found for $C_5H_{11}As$): C (41.11, 40.94), H (7.59, 7.56).

1-methylstibolane (5c): Colourless oil, bp 57-60°C (15–18 mmHg), Lit.:[13] 67-68°C (30 mmHg); 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.80–1.00 (m, 8 H), 0.52 (s, 3 H); GC-MS (m/z, %): 192 [194](M^+ 75), 177 (44), 149 (58), 136 (100); HRMS (*m*/*z*): $[M]^+$ calcd for $C_5H_{11}Sb$, 191.9899; found, 191.9897; analysis (% calcd, % found for $C_5H_{11}Sb$): C (31.13, 31.24), H (5.75, 5.77).

1-methylbismolane (5d): Colourless oil, bp 120–125°C (15–18 mmHg), Lit.:[14] ~35°C (10^{-1} mmHg); 30% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 2.60–1.80 (m, 8 H), 0.87 (s, 3 H); GC-MS (m/z, %): 280 (M^+ 20), 265 (15), 252 (10), 224 (48), 209 (100); analysis (% calcd, % found for $C_5H_{11}Bi$): C (21.44, 21.40), H (3.96, 3.91).

1-methylphosphinane (6a): Colourless oil, bp 145–147°C (760 mmHg), Lit.:[15] 146°C (760 mmHg); 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.85–1.00 (m, 10 H), 1.32 (d, 3 H, *J* = 3.0 Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$) δ (ppm)= –53.5 ppm; GC–MS (m/z, %): 116 (M^+ 100), 101 (45), 73 (50), 70 (25), 46 (63); HRMS (m/z): $[M]^+$ calcd for $C_6H_{13}P$, 116.0755; found, 116.0752; analysis (% calcd, % found for $C_6H_{13}P$): C (62.05, 62.03), H (11.28, 11.31).

1-methylarsinane (6b): Colourless oil, bp 70–75°C (15-18 mmHg), Lit.:[16] 153-155°C (760 mmHg); 60% yield; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.75–1.25 (m, 10 H), 0.90 (s, 3 H); GC-MS (m/z, %): 160 (M^+, 100), 145 (42), 69 (33); HRMS (m/z): $[M]^+$ calcd for $C_6H_{13}Sb$, 160.0233; found, 160.0230; analysis (% calcd, % found for $C_6H_{13}Sb$): C (45.02, 44.85), H (8.18, 8.15).

1-methylstibinane (6c): Colourless oil, bp 74–79°C (15-18 mmHg), Lit.:[13] 77–79°C (19 mmHg); 50% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.80–1.00 (m, 10 H), 0.66 (s, 3 H); GC–MS (m/z, %): 206 [208] (M^+ 56), 191 (39), 163 (36), 136 (100), 121 (42), 69 (82); HRMS (m/z): $[M]^+$ calcd for $C_6H_{13}Sb$, 206.0055; found, 206.0052; analysis (% calcd, % found for $C_6H_{13}Sb$): C (34.83, 34.95), H (6.33, 6.35).

1-methylbismane (6d): Colourless oil, bp 135–145°C (15–18 mmHg), Lit.:[14] ~55°C (10^{-1} Torr); 25% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 2.60–1.20 (m, 10 H), 0.89 (s, 3 H); GC-MS (m/z, %): 294 (M^+ 15), 279 (10), 224 (50), 209 (100); analysis (% calcd, % found for $C_6H_{13}Bi$): C (24.50, 24.44), H (4.45, 4.43).

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Chapter 6

ROLE OF RING AROUND THE PHOSPHORUS ATOM:

SYNTHESIS OF CYCLIC HALOALKYL PHOSPHINE AND THEIR APPLICATION

6.1 Introduction

The synthesis of cyclic phosphine derivatives is of considerable current interest principally because these compounds are the most commonly studied ligands for application in homogeneous catalysis.[1] In fact, the development of bisphosphine and phospho-amino compounds and their application to the homogeneous catalysis and coordination chemistry have increased enormously in the past decade.[1,2] Generally, the reported syntheses of 1-substituted cyclic phosphines are related to the interaction of several reagents with halophosphines[3,4] or with primary and secondary phosphines.[4-7] However, we have noted that haloalkyl derivatives of tri-coordinate phospholane and phosphinane are still unknown. In spite of this, compounds can be used in the synthesis of bidentate ligands. A possible reason for their absence in the literature could be that primary or secondary phosphanes (RPH_2 or R_2PH) cannot be used to obtain haloalkyl derivatives of cyclic phosphanes with halogen group derivatives because of the possible reactivity of the PH group with the halogen group.[8] For this reason, it is either very difficult to obtain haloalkyl cyclic phosphine derivatives with current procedures.

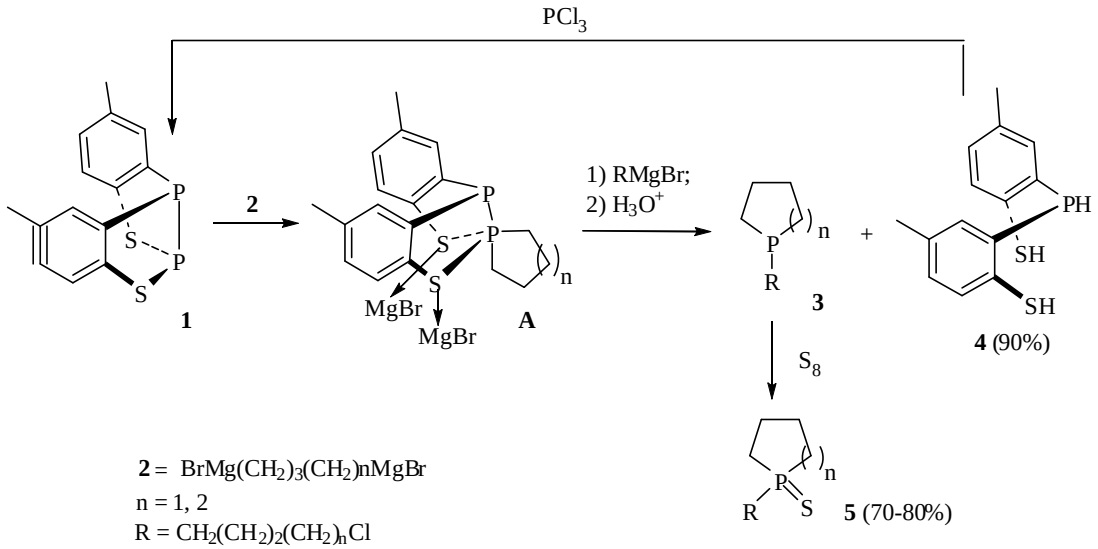
6.2 Results and discussion

Recently a new synthesis[9] of tertiary cyclic phosphines, and their sulfides, was developed using the benzothiadiphosphole **1** as a starting reagent. In fact, as reported in Chapter 4, the simultaneous or the sequential addition of equimolar amounts of a bis- and a mono-Grignard reagent RMgBr (R = alkyl, phenyl, alkenyl) to one equivalent amount of **1** gave tertiary cyclic phosphines and, after the addition

of elemental sulfur, their sulfides in good yields at room temperature. In particular a new class of 1-alkenyl derivatives of cyclic phosphines was obtained that was not possible or very difficult to obtain with the known procedures.

These results encouraged us to develop a synthetic method to obtain haloalkyl phospholanes and haloalkyl phosphinanes using our phosphorus-donating reagent **1** by the addition of bis- and a mono-Grignard reagents at room temperature. Consequently, we obtained the haloalkyl cyclophosphane derivatives **3** (70-80% yield) by addition to **1**, in the first step, of equimolar amounts of a bis-Grignard reagent **2** (n = 1 or 2), and in the second step, addition of a mono-Grignard reagent RMgBr (R = haloalkyl group). this reaction mechanism had already been studied and explained by the intervention of hypervalent phosphorus species such as the intermediate **A** (scheme 6.1).

In addition we found that the treatment of the resulting reaction mixture with acidic (HCl) water gave the cyclic tertiary phosphines **3** and the by-product **4** in 90% yield (Scheme 6.1). These two reaction products can be separated easily by treating the organic solution with aqueous NaOH; in this way the sodium salt of compound **4** dissolves in the aqueous solution, whereas the organic phase contains almost pure phosphine **3**. Compound **4** can be recovered, as reported previously,[11] from the basic aqueous layer by acidification and extraction, and then transformed to **1** for re-use. It should be noted that phosphines **3** were analyzed only by GC-MS analysis, and were not isolated. Rather they were immediately treated with sulfur to obtain the corresponding sulfides **5** (Scheme 6.1), which are stable and thus were separated by column chromatography and fully characterized.

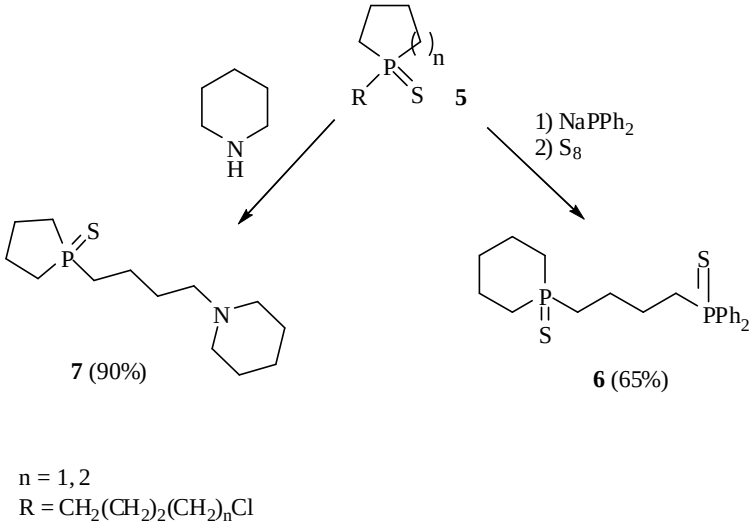


Scheme 6.1 Synthesis of haloalkyl cyclophosphane derivatives **3**, and their sulfides **5**.

As we hypothesized the presence of an halogen group in the moiety permit the use of these haloalkyl cyclophosphane derivatives **3** in the synthesis of bidentate ligands. In fact, the high reactivity of the chlorine group as a living group easily permits substitution by secondary phosphines and amines.

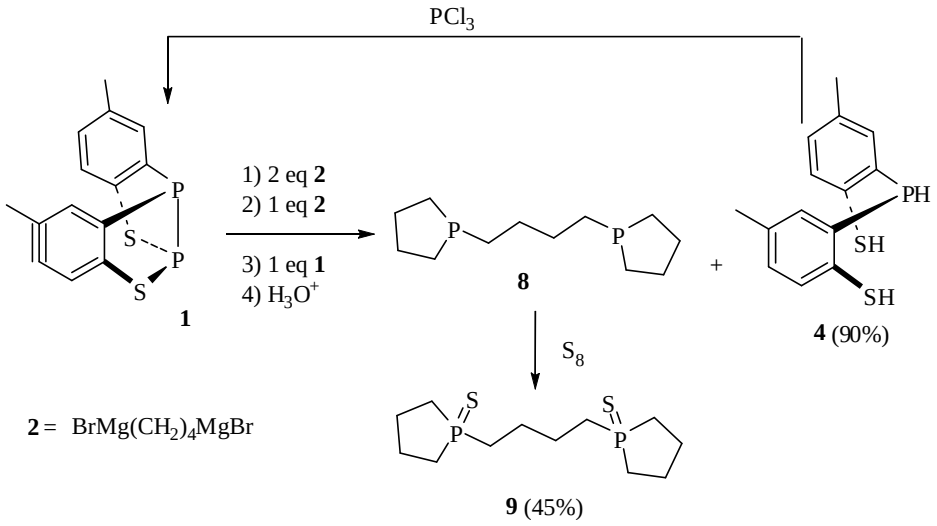
For the synthesis of the bisphosphine **6**, the compound **5b** was treated with a solution of sodium diphenyl phosphine. After treatment of the reaction mixture with elemental sulfur, compound **6** was obtained in moderate yields (65%) (scheme 6.2) and purified by column chromatography and fully characterized.

Also phospho-amino compound **7** can be synthesized using **5a** which was treated with piperidine in toluene at reflux. Compound **7** was obtained in high yield (90%) (scheme 5.2) and purified by column chromatography and fully characterized.



Scheme 6.2 Synthetic application of haloalkyl cyclophosphines.

Alternatively we optimized a one-pot three-step procedure for the synthesis of a C_2-symmetric bisphospholane compound. We obtained bisphospholane **8** by addition, in the first step, of two equimolar amounts of bis-Grignard reagent **2** to one of reagent **1**; in the second step another equimolar amount of bis-Grignard reagent **2** was added to the reaction mixture, finally in the third step, a dropwise addition of one equimolar amount of **1** was performed (scheme 6.3). After quenching the reaction mixture with acidic water we obtained the bisphospholane **8** and the end product **4** (90% yield, respect to **1**). The two compounds were easily separated as previously described. After separation, the bisphospholane **8** was immediately treated with elemental sulfur, giving the sulphide 9 in moderate yield (45%), which was purified by column chromatography and fully characterized.



Scheme 6.3 Synthesis of bisphospholane **8** and sulfide derivative **9**.

6.3 Experimental section

6.3.1 General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300 (400), at 76.46 (100.56) and 120.76 (161.89) MHz, respectively. Chemical shifts are referenced to internal standard TMS (^{1}H NMR), to solvent (77.0 ppm for ^{13}C NMR) and to external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. MS spectra were recorded at an ionisation voltage of 70 eV. Flash chromatography (FC) was performed on silica gel (0.040-0.063 mm). Melting points are uncorrected. THF was distilled from sodium benzophenone ketyl and all solvents were purified appropriately before use and degassed immediately prior to use. All Grignard reagents used, both commercially available and prepared from the corresponding alkyl halide or alkyl dihalide[12] and magnesium turnings, were titrated immediately prior to use by standard methods.[13] Air and moisture sensitive solutions and reagents were handled in a dried apparatus under a dry argon atmosphere using standard Schlenk-type techniques.

6.3.2 General one-step procedure for the synthesis of cyclic tertiary haloalkyl phosphine sulfides

The bis-Grignard reagent (1.1 mmol) was added to a solution of **1** (1 mmol) in THF (10 mL), at room temperature. The mixture was stirred for 15 min, then the mono-Grignard reagent (1.1 mmol) was added. The reaction mixture was stirred for 1 h after that the solvent was partially evaporated and the reaction mixture was treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 gave a mixture of phosphines and the residue **3**. The phosphines were easily separated from 3 by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of **4** was dissolved in the aqueous solution, whereas the phosphines were in the organic phase. Treatment of this layer with a slight excess of elemental sulfur gave the corresponding sulfides, which were purified by flash chromatography (dichloromethane: petroleum ether 3:2) and fully characterized. Compound 4[10] was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and was then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **4** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent **1** in almost pure form, allowing it to be reused without further purification.

1-(4-chlorobutyl) phospholane sulfide (**5a**): y = 80%, colourless oil, R_F = 0.44 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.58 (t, 2 H, *J*=5.6 Hz, CH_2Cl), 2.20-1.74 (m, 14 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.1 (s), 33.2 (d, *J*=52 Hz), 33.1 (d, *J*= 15 Hz), 32.8 (d, *J*=47 Hz), 26.0 (d, *J*=6 Hz), 20.5 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 64.5 (m) ppm; MS (70 eV, EI): *m/z* : 212 (M^+,9), 210 (26), 175 (100), 120 (99); IR: 598 (CCl), 725 (PS), 1111 (PC) cm^{-1}.

1-(4-chlorobutyl) phosphinane sulfide (**5b**): y = 82%, grease solid, R_F = 0.38 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.58 (t, 2 H, *J*=6.1 Hz, CH_2Cl), 2.20- 1.50 (m, 16 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.2 (s), 33.3 (d, *J*=15 Hz) , 30.9 (d, *J*=48 Hz), 30.0 (d, *J*=50 Hz), 26.4 (d, *J*=6Hz), 21.9 (d, *J*=6 Hz), 19.3 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 37.8 (m) ppm; MS (70 eV, EI): *m/z* : 226 (M^+, 6) 224 (18), 189 (100), 134 (53); IR: 595 (CCl), 728 (PS), 1110 (PC) cm^{-1}.

1-(5-chloropentanyl) phospholane sulfide (**5c**): y = 73%, grease solid, R_F = 0.43 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.56 (t, 2 H, *J*=6.6 Hz, CH_2Cl), 2.20-1.40 (m, 16 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.7 (s), 33.4 (d, *J*=47 Hz), 33.2 (d, *J*=52 Hz) , 32.0 (d, *J*=15Hz), 26.0 (d, *J*=6Hz), 22.4 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ =

64.6 (m) ppm; MS (70 eV, EI): *m/z* : 226 (M^+ , 8), 224 (24), 189 (81), 120 (100); IR: 598 (CCl), 724 (PS), 1109 (PC) cm^{-1}.

1-(5-chloropentanyl) phosphinane sulfide (**5d**): y = 75%, grease solid, R_F = 0.40 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.56 (t, 2 H, *J*=6.4 Hz, CH_2Cl), 2.20-1.40 (m, 18 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.7 (s), 32.1(s), 30.9 (d, *J*=49 Hz), 30.6 (d, *J*=51 Hz), 28.0 (d, *J*=15 Hz), 26.4 (d, *J*=6 Hz), 21.9 (d, *J*=6 Hz), 21.1 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 38.7 (m) ppm; MS (70 eV, EI): *m/z* : 240 (M^+ , 5), 238 (15), 203 (91), 134 (100).; IR: 595 (CCl), 725 (PS), 1111 (PC) cm^{-1}.

6.3.3 Synthesis of 1-[4-(diphenylphosphorathioyl)butyl]-phosphinane 1-sulfide (6)

To a solution of diphenyl phosphine (0.689 mmol) in THF (4 ml) was added metallic sodium (0.013 mol) at 0°C, than the mixture was stirred for 5 h at room temperature. After that the resulting orange-red solution was dropwise added under argon to a solution of 1-(4-chlorobutyl) phosphinane sulfide (5b) (0.53 mmol) in THF (4 ml). The reaction mixture was stirred for 1 h than was treated with a slight excess of elemental sulfur to give the corresponding sulfides, which were purified by flash chromatography (dichloromethane: petroleum ether 3:2) and fully characterized.

1-[4-(diphenylphosphorathioyl)butyl]-phosphinane 1-sulfide (**6**): y = 65 %, yellow solid, pf = 134-136 °C, R_F = 0.14 (dichlromethane); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): □ = 7.86-7.78 (m, 4 H), 7.54-7.42 (m, 6 H), 2.55-2.44 (m, 2 H), 2.12-1.40 (m, 16 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): □ = 21.8 (d, $^2J_{PC}$=6.48 Hz,), 22.6 (dd, J_{PC}=17.8 Hz, J_{PP}=3.3 Hz), 23.3 (dd, J_{PC}=16.2 Hz, J_{PP}=2.4 Hz), 26.2 (d, $^2J_{PC}$= 6.5 Hz), 30.2 (d, $^1J_{PC}$= 50.2 Hz), 30.8 (d, $^1J_{PC}$= 48.6 Hz), 32.1 (d, $^1J_{PC}$= 57.0 Hz), 128.6 (d, J_{PC} =12.1 Hz), 130.9 (d, J_{PC} = 9.7 Hz), 131.5 (d, J_{PC} =3.2 Hz), 132.5 (d, J_{PC} = 80.14 Hz) ppm; ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): □ = 38.5, 43.0 ppm; IR: 716 (PS), 1439 (P-Ph), 2863 (Ph) cm^{-1}.

6.3.4 Synthesis of bidentate ligands

A solution of chlorophosphine sulphide (**5**) (1 mmol) and amine (piperidine, pirrolidine, morpholine) (3 mmol) in toluene (10 ml) was refluxed for 20 h. After that the solvent was partially evaporated and the reaction mixture was treated with water and extracted with CH_2Cl_2. The organic layer, containing the product, was purified by flash chromatography (dichloromethane) and the product fully characterized.

1-[4-(1-sulfidophospholan-1-yl)butyl] piperidine (**7**): y = 90%, grease solid, R_F = 0.0 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.50-1.40 (m, 26 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 57.9, 54.1, 33.4 (d, *J* = 52 Hz), 33.1 (d, *J* = 47 Hz), 29.7, 26.0 (d, *J* = 6 Hz), 24.5, 23.4, 21.0 (d, *J* = 3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 64.7 (m) ppm; MS (70 eV, EI): *m/z* : 259 (M^+, 2), 226 (13), 175 (3), 143 (13), 98 (100).

6.3.5 One-step procedure for the synthesis of cyclic tertiary bis-phosphine

A solution of **1** (1 mmol) in THF (10 mL) was added drop wise to a solution of bis-Grignard reagent (2 mmol) in THF (5 ml), at room temperature. The mixture was stirred for 2 h, then again the bis-Grignard reagent (1 mmol) was added to the resulting solution. After that to the reaction mixture was added drop wise a solution of **1** (1 mmol) in THF (10 mL), and stirred for 4 h. During the 4 h, the reaction was monitored by GC-MS. After that the solvent was partially evaporated and the reaction mixture was treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 gave a mixture of diphosphine and the residue **4**. The diphosphine was easily separated from **4** by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of 4 was dissolved in the aqueous solution, whereas the diphosphine was in the organic phase. Treatment of this layer with a slight excess of elemental sulfur gave the corresponding sulfides (**9**), which were purified by flash chromatography (dichloromethane: petroleum ether 3:2) and fully characterized. Compound 4 was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and was then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **4** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent 1 in almost pure form, allowing it to be reused without further purification.

1,1'-butane-1,4-diylbis(phospholane) 1,1'-disulfide (**9**)[14]: y = 45%, brown solid, pf = 29°C; p.eb. = 115-120°C (0.1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.7-2.1 (m, 24 H) ppm ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$, 25 °C): δ = 24.0 (2C, dd, $^{2}J_{PC}$ = 3 Hz, $^{1}J_{PC}$ = 15 Hz), 26.0 (4C, d, $^{2}J_{PC}$ = 6 Hz), 33.2 (2C, d, $^{1}J_{PC}$ = 45 Hz), 33.5 (4C, d, $^{1}J_{PC}$ = 52 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 63.2 ppm; MS (70 eV, EI): *m/z* : 294 (M^+,14), 175 (66), 119 (58), 85 (27), 63 (100), 55 (59), 41 (46); IR: 715.78 (PS), 1113 (PC) cm^{-1}.

6.4 References

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Chapter 7

ROLE OF THE PENTACOORDINATION OF PHOSPHORUS:

WITTIG MECCHANISM

7.1 Introduction

Since its discovery, about 60 years ago,[1] the Wittig reaction plays a central role in organic synthesis, for its ability to form a carbon-carbon double bond with high positional selectivity, relatively high chemoselectivity, and may be conducted in many cases with reliable and high stereocontrol.[2]

Originally, little attention was paid to stereochemistry since several olefins were obtained as *E/Z* mixtures, suggesting that the reaction might not be generally stereoselective. However, it was soon discovered that the type of ylide and the reaction conditions could play a key role in determining the reaction stereochemistry. For example, non-stabilized phosphorus ylides react with aldehydes to give largely *Z* alkenes, except under special conditions,[3] and stabilized ylides give predominantly *E* alkenes, but semi–stabilized ylides generally give a mixture of *E*/*Z* alkenes with a relative ratio around 50/50. For these reasons the mechanism has been the subject of extensive experimental[4] and theoretical[5a] investigations, and has been comprehensively reviewed.[4,5b]

These studies have shown that the Wittig reaction is influenced by many factors: type of ylide (stabilized, non-stabilized or semi-stabilized), substituents on the phosphorus atom, presence of lithium salts, solvent, temperature,[2b,2c,6] and concentration.[7e] Because it is now demonstrated[2a,7] without doubts that 1,2-oxaphosphetanes, cyclic phosphorus pentacoordinated compounds with trigonal bipyramidal structure, are central intermediates in the Wittig reaction, for better understand the mechanism involved in this reaction it is of fundamental importance to know the chemistry of pentacoordinated phosphorus compounds focusing particular attention to all the factors which influence the stability and the decomposition of cyclic pentacoordinated phosphorus trigonal bipyramidal intermediates.

Up to date, an inclusive rule for explain the stereoselectivity in the Wittig reaction is difficult to formulate because the large number of data reported in important works[2a] are often in apparent contrast. We think that this is due to the different reaction conditions used and to the fact to have studied the Wittig reaction as a simple cycloaddition reaction between the ylide and the carbonyl group. Instead, it is of preminent importance to analyze all the factors which determine the stability of the four cyclic phosphorane intermediates, the so-called "1,2–oxaphosphetanes" (2,2,2–trisubstituted-1,2 λ^5–oxaphosphetanes) depicted in Scheme 1. Considerable information is now available[8] on the factors which affect the stability of such trigonal bipyramidal phosphorane derivatives and control the process of ligand reorganization within them. Two factors turn out to be important in this connection: (a) the preference of electronegative groups for the apical positions and (b) the preference of a small membered ring for an apical-equatorial situation. However, the stereochemistry of the reaction is also dependent on the steric interactions, as well as on the specific reaction conditions.

It is about forty years that our group is studying reactions in which cyclic pentacoordinated phosphorus compounds are involved as intermediates determining also the different stereochemical results. In one case we have demonstrated[9a] that an highly stereoselective result was due to different decomposition rates of two *cis*/*trans* cyclic isomeric trigonal bipyramidal phosphorane intermediates, which were in equilibrium between them. In another work[9b] we have observed that *cis* hexacoordinated phosphorane intermediates, being less stable than the trans forms, immediately collapse determining a stereoselective result. The high decomposition rate of the *cis* pentacoordinate intermediate, caused by its major overcrowding, permits its highly stereoselective evolution towards the final product. In addition, Vedejs et al. observed that *cis*-isomer of oxaphosphetanes from non-stabilized ylides decomposed faster than did the trans-isomers.[10b,c]

For this reason we started a study on the Wittig reaction using both, triphenylphosphorus non-stabilized and stabilized ylides with different aldehydes in which only the steric effect might influence the different stereochemical results. In other words, we will see if only the steric factor may influence and consequently explain the possible high stereoselective formation of alkenes.

7.2 Results and discussion

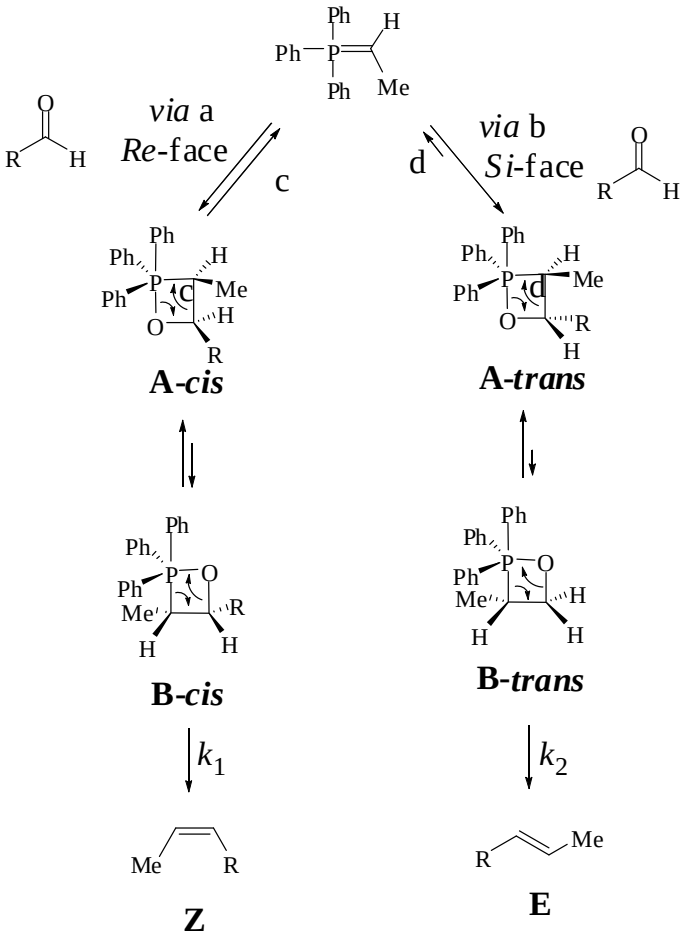
7.2.1 Case of non-stabilized ylides

The reaction mechanism, qualitatively outlined in Scheme 7.1, we now propose to study is in line with several previous important studies.[7]

The first attack is a cycloaddition of the carbonylic group on the ylide to give pentacoordinate oxaphosphetane intermediates with trigonal bipyramidal structures.

It is well known from over 40 years that, when it possible, the formation of a cycle around a pentacoordinate phosphorus atom is favoured 10^{6-8} fold with respect to the formation of acyclic intermediates.[11] Then, the formation of a phosphorus cyclic pentacoordinated intermediate is largely favourite with respect to any other type of possible intermediate. In other words, the attack of the ylidic carbon on the carbonyl carbon to form cyclic oxaphosphetanes is favoured of a factor 10^{6-8} over any other nucleophilic attack.[11]

The stereochemical outcome of the reaction can be explained by the characteristics that govern pentacoordinate forms. The most favourite structure for a pentacoordinate form is the trigonal bipyramidal geometry. The relative position of the substituents in pentacoordinate compounds respects rules depending from their steric hindrance and apicophilicity.[12]



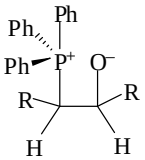
Scheme 7.1. Mechanistic proposal for non-stabilized ylides. Another set of oxaphosphetane intermediates, isomers of structures **A** and **B**, is possible. However, as a rule, four-member rings are unable to occupy the diequatorial position of trigonal bipyramid and, therefore, only isomers **A** and **B** with apical-equatorial rings are considered to participate in this mechanism.

Keeping in mind these considerations and that the carbonyl compound can attack the ylide in two ways (Scheme 7.1, *via a* or *via b*), we think that this attack brings at two possible pentacoordinate intermediates with trigonal bipyramidal structures, namely **A-*cis*** and **A-*trans***, which have the oxygen atom in apical position. This idea is derived from the general rule of "apical entry/apical departure" for nucleophilic substitution reactions at pentacoordinated phosphorus with trigonal bipyramidal structures;[8c] it is also known that the departure of the apical group occurs firstly.

In this manner, decomposition of these **A** isomers should give the starting reagents and the *cis*-isomer of **A** oxaphosphetanes should decompose faster than the *trans*-isomer. This enhances the reversibility of the step which forms the *cis*-oxaphosphetane compared to that forming the *trans*-oxaphosphetane. In other words, the retro-Wittig reaction should be favored for the **A-*cis*** intermediate with respect to the **A-*trans***.

These inferences suggest that, when intermediates **A-*cis*** and **A-*trans*** are sufficiently long-lived species, they must be in equilibrium with starting materials, by a retro-Wittig reaction, and therefore among them.[10,3a,7a,7c] (For example, Maryanoff *et al.* report that the intermediates derived from hexanal and triphenylphosphonium ylides are formed reversibly[10a]). In this manner the **A-*trans*** is favoured by thermodynamic factors. To bring to the final alkenes, the **A** intermediates must complete a pseudorotation[8h,12] to give two new pentacoordinate species **B-*cis*** and **B-*trans***, with the oxygen atom in equatorial position and the P–C bond in apical position. Since the oxygen atom prefers to be in apical position, **B** species are more disfavoured and unstable than **A** species. In addition, in these **B** species the equatorial oxygen maximizes the back–bonding donation of the oxygen atom thus favoring the decomposition to alkene and triphenylphosphine oxide. The driving force of this decomposition is given by the propensity of the oxygen atom to form a double bond with the phosphorus atom.

It has to be noted that our mechanism doesn't foresee formation of betainic intermediates as those shown in Figure 7.1 for the reason that these intermediates have been only hypothesized (they have only a historical value[2a]), but never detected in the course of the reaction; a further confirmation and, at the same time, an explanation of no formation of such a betainic intermediates is given by the very strong affinity of the phosphorus atom with the oxygen atom that makes very unlikely the existence of a zwitterionic species that bears these two atoms with opposite charges.

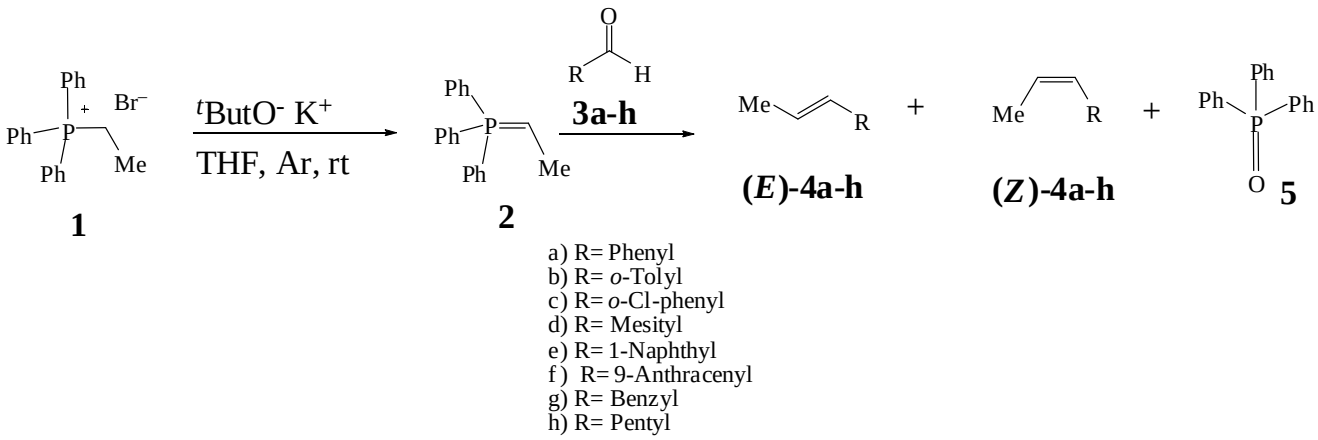


Betaine

Figure 7.1. Betainic form

Stereoselection is driven by the irreversible decomposition of the **B** intermediates, which have a different rate of collapse[10] due to their different stability. In fact, the **B-*cis*** isomer (whose formation, as we have previously said, is disfavoured and therefore its quantity should be smaller in comparison with the **B-*trans*** form) is more unstable because of the greatest steric hindrance and collapses to form the *Z* olefin very quickly with respect to the **B**-*trans* pentacoordinate intermediate. This rapid decomposition of the **B-*cis*** pentacoordinate intermediate brings to increase the quantity of the *Z* olefin, because the other steps of the reaction are in equilibrium and the system has the tendency to return to the equilibrium by reversal reaction.

Then, in order to verify the above mechanism and to better understand the outcome of the Wittig reaction we studied the influence of the steric hindrance on the carbonyl compound. In particular, we have studied the reaction using the non-stabilized ylide **2** with aldehydes **3 a–h**, with different steric hindrance (Scheme 7.2).



Scheme 7.2. Reaction with non–stabilized ylide **2.**

Olefins **4a–h** have been obtained in different *E*/*Z* ratios by reaction between triphenylethylphosphonium bromide **1** and potassium *tert*-butylate, to obtain ethylidene(triphenyl)phosphorane **2**, followed by addition of the aldehydes **3a–h**, (Scheme 7.2). The isomeric ratio was calculated by GC-MS spectroscopy in the reaction mixture without purification. The isomeric ratios are reported in Table 7.1.

Table 7.1. Reactions of non-stabilized ylide **2** and stabilized ylide **7** with differently hindered aldehydes.

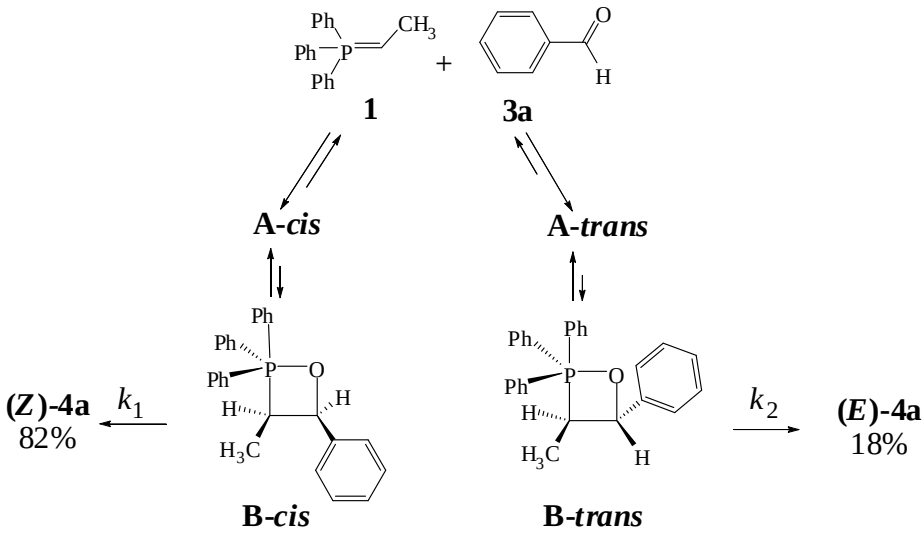
Entry	Ylide	Aldehyde (R)	Products	*E*/*Z* ratio[a]
1	**2**	**3a** (phenyl)	**4a** (*E*+*Z*)	18/82
2	**2**	**3b** (*o*-tolyl)	**4b** (*E*+*Z*)	16/84
3	**2**	**3c** (*o*-Cl-phenyl)	**4c** (*E*+*Z*)	24/76
4	**2**	**3d** (mesityl)	**4d** (*E*+*Z*)	48/52
5	**2**	**3e** (1-naphthyl)	**4e** (*E*+*Z*)	15/85
6	**2**	**3f** (9-anthracenyl)	**4f** (*E*+*Z*)	49/51
7	**2**	**3g** (benzyl)	**4g** (*E*+*Z*)	10/90
8	**2**	**3h** (pentyl)	**4h** (*E*+*Z*)	13/87
9[b]	**2**	**3a**	**4a** (*E*+*Z*)	11/89
10[b]	**2**	**3d**	**4d** (*E*+*Z*)	33/67
11	**7**	**3a**	**8a** (*E*+*Z*)	96/4
12	**7**	**3b**	**8b** (*E*+*Z*)	95/5
13	**7**	**3c**	**8c** (*E*+*Z*)	93/7

[a] *E*/*Z* ratio calculated by GC-MS spectroscopy. [b] The reaction is carried out at 0 °C. All the other reactions are carried out at room temperature.

As shown in Table 7.1, variation of steric hindrance on the aldehydic compound gives a variation of the *E*/*Z* ratio in the final products.

These results could be explained by comparing the structure of the pentacoordinate intermediates, such as **A** and **B**, formed during the course of the reaction.

In particular, using benzaldehyde **3a**, the corresponding **B**-***cis*** pentacoordinate intermediate (Scheme 7.3), is more unstable than the *trans* one, and then it collapses immediately after its formation ($k_1 >> k_2$), shifting the equilibrium in favour of the *cis* structure, giving a great predominance of the olefin type *Z*.



Scheme 7.3. Reaction between ylide **1** and benzaldehyde **3a**.

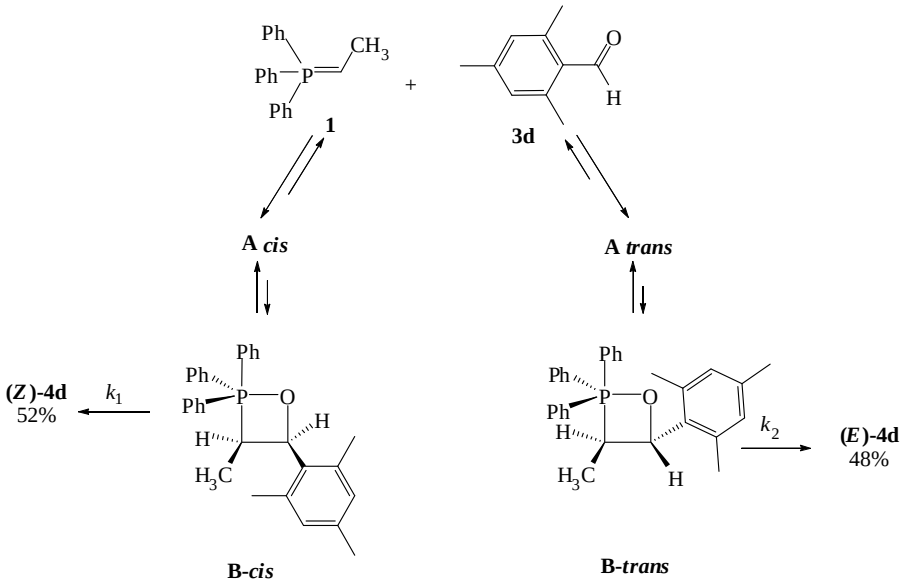
In the reaction with *ortho*-tolylaldehyde (**3b**), the overcrowding on the pentacoordinate intermediates is similar to those found in the reaction with benzaldehyde, bringing to a little increase of the *E*/*Z* ratio in favour of *Z* olefin ($k_1>>k_2$).

On the contrary, when a more hindered compound as mesitaldehyde (**3d**) is used (Scheme 7.4) the overcrowding on the pentacoordinated intermediate becomes very high, both for the *cis* intermediate and the *trans*, which collapse with similar rate (k1~k2), bringing to a drastic increase of the E/Z ratio (48/52).

It should be noted that the ratio E/Z is also depending from the reaction temperature.

In fact, when we carried out the reaction with **3a** at 0 °C (Table 7.1, entry 9) we obtained a ratio E/Z of 11/89 while at room temperature the ratio was 18/82 confirming again that **B-*cis*** oxaphosphetane have a superior rate of decomposition with respect to the *trans* one.

The same considerations are worth for all reactions with other aldehydic compounds.



Scheme 7.4. Reaction between ylide **1** and mesytaldehyde **3d**.

7.2.2 Variable Temperature ^{31}P NMR study

To complete this investigation we have carried out a study at ^{31}P NMR spectroscopy in order to observe the *cis* and *trans* oxaphosphetane intermediates of the above reaction between non-stabilized phosphorus ylide and aldehydes.

Typical experiment was carried out with ethyltriphenylphosphonium bromide (**1**) under argon. The salt **1**, suspended in dry tetrahydrofuran was treated with potassium tert-butylate at 25 °C to generate the ylide, evidenced in the relative ^{31}P NMR spectrum as a sharp singlet at 15.1 ppm. Addition, directly in the NMR tube at –78°C, of an equimolar amount of benzaldeyde to the above reaction mixture produced a spectrum with two signals in the region of pentacoordinate species, –60.6 ppm (*cis*-oxaphosphetane, probably the form **A**) and –60.7 ppm (*trans*-oxaphosphetane, probably the form **A**). The *cis*/*trans* ratio was about 9/91 and this high preference for the trans isomer was predicted on the basis of the rules which govern the phosphorus pentacoordination.[8] It should be noted that the *cis* and *trans* configuration was unequivocally determined by Maryanoff.[7c] By increasimg the temperature of the NMR probe until –30 °C, a new singlet arose at 29.3 ppm was detected, due to the formation of triphenylphosphine oxide. At the end of the reaction the ratio between Z/E olefins was 82/18, which did not reflect the original ratio of *cis*/*trans* oxaphosphetanes (9/91). Probably this is due to the conversion of *trans* to *cis* oxaphosphetane during the process by retro-Wittig. Our assignement of the signals to *cis* and *trans* oxaphosphetanes (–60.6 ppm for *cis*-oxaphosphetane and –60.7 ppm for *trans*-oxaphosphetane) corresponds to the assignement made by Maryanoff and

determined via chemical argument. However, it should be noted that the ratio between *cis* and *trans* oxaphosphetanes reported by Maryanoff was 4:1 in contrast with our result of 1:9. But this is certainly due to the contamination of reagents such as hexamethyldisilazide which can interfere with the stability of oxaphosphetanes and probably this interference determine also a small difference of their ^{31}P NMR chemical shifts (–61.2 ppm and –61.6 ppm).

The low temperature experiments has been performed also for the aldehydes **3b** and **3d**. In the reaction with the aldehyde **3b**, the ^{31}P NMR spectrum showed the presence of two peaks at –61.1 ppm and –61.8 ppm in a relative ratio of 10/90, ascribed (by analogy with the reaction with benzaldehyde **3a**) to *cis* and *trans* oxaphosphetanes.

In the reaction with the aldehyde **3d**, the ^{31}P NMR spectrum showed the presence of two peaks at –61.6 ppm and –62.0 ppm in a ratio of 27/73 respectively, ascribed (by analogy with the reaction with benzaldehyde **3a**) to *cis* and *trans* oxaphosphetanes in a mixture of **A** and **B** isomers.

Then we will obtain always the prevalence of the Z olefin because a *cis*-oxaphosphetane is much more unstable than the *trans* one. The *E*/*Z* ratio in this case depends only on the steric effects which are very crucial in pentacoordinated compounds in causing the instability of these hypervalent species.

As result of the different decomposition rates, if we want to further increase the amount of the *Z* olefin is enough to carry out the reaction at lower temperatures (see Table 7.1, entries 9 and 10).

This consideration would seem applicable only at the non-stabilized ylide, which bring to favour the formation of the *Z* olefin.

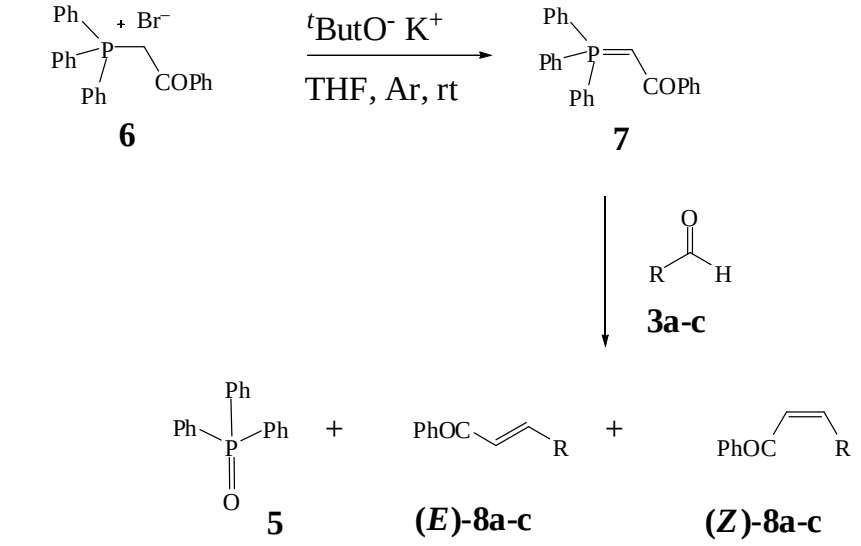
Now we wish to evaluate if our mechanistic proposal might give a possible explanation also of the high *E* selectivity obtained with stabilized ylides.

7.2.3 Case of stabilized ylides

Stabilized ylides have been the subject of numerous mechanistic studies,[2a,2d,4d,13 marinoffref] but none have shown evidence for oxaphosphetane intermediates. Probably, the related intermediate adducts are difficult to form at low temperature while at room temperature they decompose to alkenes too rapidly for their detection.

In Scheme 7.5 are reported the reactions which have been carried out between the stabilized ylide **7** (1-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one), and aldehydes **3a–c**.

In table 7.1, entries 11–13, the *E*/*Z* ratios of obtained olefins **8a–c** are reported.



a) R= Phenyl
b) R= *o*-Tolyl
c) R= o-Cl-phenyl

Scheme 7.5. Reactions with stabilized ylide **7.**

The reactions were carried out in the same experimental conditions of the above reported reactions with non-stabilized ylides.

It should be noted that the reactions carried out at room temperature gave product yields lower with respect to those carried out at higher temperature (50°C). However, the ratio *E*/*Z* remain always the same. Firstly, we carried out the reactions at room temperature hoping that in these conditions the intermediate adducts might be detected and for this purpose we monitored the reaction at room temperature through ^{31}P NMR spectroscopy. Since no intermediate have been detected in these conditions, we tried to identify the oxaphosphetanes intermediates by reaction at lower temperature (–100 °C and 0 °C) between ylide **7** and aldehyde **3a**. Unfortunately, also in these cases, no detection of *cis*- and *trans*-oxaphosphetanes was observed.

We have obtained always an high *E* stereoselectivity (see entries 11–13 in Table 7.1), but in these cases it is not possible to affirm that an equilibration between *cis*- and *trans*-oxaphosphetanes occurs.

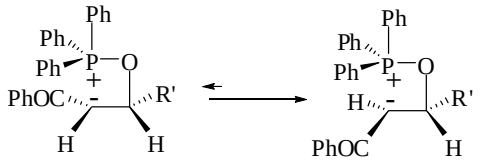
Probably, in the case of stabilized ylides, the oxaphosphetanic intermediates **B** (*cis* and *trans*) are more favored with respect to the corresponding oxaphosphetanes **A** (in contrast with that occurring in the non-stabilized ylides). This is due to the presence of the electron-withdrawing group on the ylidic moiety that strongly enhances the apicophilicity[12] of the carbon atom bound to the phosphorus atom, thus favoring the apical position of the group bound to this carbon atom. In addition, it is more probable that the formation of the **B-*trans*** intermediate is favoured with respect to **B-*cis*** one. This is accord with that occurs in non-stabilized ylides in which the corresponding **B-trans** is favored with respect to **B-*cis*** (the ratio of the two ^{31}P NMR signals of oxaphosphetanes **B-*trans*** and **B-*cis*** was

90/10 for the case aldehyde CCC or 70/30 for the cases of aldehyde HHH). In addition, the presence of the electron-withdrawing group permits a very fast decomposition of these oxaphosphetanes, explaining the difficulty to detect these intermediates in the ^{31}P NMR spectra.

It should be noted that the ratio E/Z for olefins **8a–c** (entries 11–13 of Table 7.1) are very similar (96/4, 95/5, 93/7), indicating that in these cases steric effects have no influence on the ratio *E*/*Z*.

In addition, in the cases of stabilized ylide the form **B** may be in equilibrium with the zwitterionic species (see Figure 7.2), stabilized by the electron withdrawing group, in which the *trans* isomer is favored giving preferentially the *E* olefin. However, it should be noted that no zwitterionic species are detected in the ^{31}P NMR spectra. Even if such a species are formed, they could be at very low concentration, not sufficient for their detection, as it occurs with oxaphosphetanes.

Then, on the basis of these data we can propose for the stabilized ylides a mechanism very similar to that described in Scheme 7.1 for non-stabilized ylides, with the difference that the equilibrium between the intermediate isomers **A** and **B** is shifted towards the isomers **B** which collapses very fast to the final olefins, prior to re-equilibrate with **A** forms. Then, in the case of stabilized ylides the retro-Wittig is practically inexistent.



Cis-zwitterionic form *Trans*-zwitterionic form

Figure 7.2. Hypothetic zwitterionic forms

7.3 Experimental section

7.3.1 General

^{31}P NMR spectra were recorded on Varian Mercury 400 or Inova 600 spectrometers, operating at 161.89 or 242.77 MHz, respectively.

Chemical shifts are referenced to external standard aq. 85% H_3PO_4. *J* values are given in Hz. GC-MS analyses were performed on an gas chromatograph equipped with a (5%-phenyl)-ethylpolysiloxane column (30 m length, 0.250 mm i.d., 0.25 μm thickness), interfaced to a quadrupole mass detector.

Mass spectra were recorded at an ionisation voltage of 70 eV in the EI mode. THF was distilled from sodium/benzophenone etyl, and all solvents were purified appropriately and degassed immediately prior to use. Air- and moisture-sensitive solutions and reagents were handled in dried apparatus under dry Argon using standard Schlenk-type techniques.

All products herein reported are known compounds and their chemico-physical data agree with those of authentic commercial samples (**(*Z*)-4a, (*E*)-4a, (*Z*)-4h, (*E*)-4h, (*Z*)-8a** and **(*E*)-8a**), or (for cases **(*Z*)-4b,**[14] **(*E*)-4b,** [14] **(*Z*)-4c,** [15] **(*E*)-4c,** [16] **(*Z*)-4d,** [17] **(*E*)-4d,** [17] **(*Z*)-4e,** [18] **(*E*)-4e,** [18] ***(Z*)-4f, (*E*)-4f,** [19] **(*Z*)-4g,** [20] **(*E*)-4g,** [20] **(*Z*)-8b, (*E*)-8b,** [21] **(*Z*)-8c** and **(*E*)-8c**[22]) with those reported in the literature.

7.3.2 Wittig reaction. General method

Potassium *tert*-butylate (89.6 mg, 0.8 mmol) was added to a mixture of triphenylethyl phosphonium bromide (300 mg, 0.8 mmol) [or 373 mg (0.8 mmol) of phenacyltriphenylphosphonium bromide] in dry THF (3 mL). The colour of the mixture became orange. After 5 minutes 1 equivalent of aldehyde (0.8 mmol) was added. The reaction became instantly white. The reaction course was monitored by GC-MS spectroscopy.

(1*Z*)–prop–1–en–1–ylbenzene (*Z*)-4a: major product. MS (70 eV, EI): *m*/*z* (%) = 118 (M^+, 71), 117 (100), 115 (41), 103 (9), 91 (31), 77 (7), 63 (7), 51 (7).

(1*E*)–prop–1–en–1–ylbenzene (*E*)-4a: minor product. MS (70 eV, EI): *m*/*z* (%) = 118 (M^+, 70), 117 (100), 115 (40), 103 (9), 91 (30), 77 (7), 65 (9), 51 (9).

1–methyl–2–[(1*Z*)–prop–1–en–1–yl]benzene (*Z*)-4b: major product. MS (70 eV, EI): *m*/*z* (%) = 132 (M^+, 63), 117 (100), 115 (50), 105 (5), 91 (26), 77 (8), 65 (8), 51 (6).

1–methyl–2–[(1*E*)–prop–1–en–1–yl]benzene (E)-4b: minor product. MS (70 eV, EI): *m*/*z* (%) = 132 (M^+, 61), 117 (100), 115 (47), 105 (12), 91 (26), 77 (9), 65 (10), 51 (7).

1–chloro–2–[(1*Z*)–prop–1–en–1–yl]benzene (*Z*)-4c: major product. MS (70 eV, EI): *m*/*z* (%) = 152 (M^+, 46), 117 (100), 115 (87), 101 (5), 91 (11), 75 (10), 63 (11), 57 (9), 51 (6).

1–chloro–2–[(1*E*)–prop–1–en–1–yl]benzene (*E*)-4c: minor product. MS (70 eV, EI): *m*/*z* (%) = 152 (M^+, 49), 117 (100), 115 (83), 101 (4), 91 (15), 75 (9), 63 (11), 57 (9), 51 (8).

1,3,5–trimethyl–2–[(1*Z*)–prop–1–en–1–yl]benzene (*Z*)-4d: major product. MS (70 eV, EI): *m*/*z* (%) = 160 (M^+, 58), 145 (100), 128 (26), 115 (20), 105 (12), 91 (11), 77 (8).

1,3,5–trimethyl–2–[(1*E*)–prop–1–en–1–yl]benzene (*E*)-4d: minor producr. MS (70 eV, EI): *m*/*z* (%) = 160 (M^+, 67), 145 (100), 128 (23), 115 (17), 105 (11), 91 (9), 77 (6).

1–[(1*Z*)–prop–1–en–1–yl]naphthalene (*Z*)-4e: major product. MS (70 eV, EI): *m*/*z* (%) = 168 (M^+, 49), 153 (100), 139 (8), 128 (4), 115 (10), 83 (5), 76 (3).

1–[(1*E*)–prop–1–en–1–yl]naphthalene (*E*)-4e: minor product. MS (70 eV, EI): *m*/*z* (%) = 168 (M^+, 51), 153 (100), 139 (6), 128 (5), 115 (11), 83 (9), 76 (4).

9–[(1*Z*)–prop–1–en–1–yl]anthracene (*Z*)-4f: major product. MS (70 eV, EI): *m*/*z* (%) = 218 (M^+, 75), 203 (100), 189 (11), 108 (9), 101 (14).

9–[(1*E*)–prop–1–en–1–yl]anthracene (*E*)-4f: minor product. MS (70 eV, EI): *m*/*z* (%) = 218 (M^+, 76), 203 (100), 189 (10), 108 (9), 101 (12).

(2*Z*)–but–2–en–1–ylbenzene (*Z*)-4g: major product. MS (70 eV, EI): *m*/*z* (%) = 132 (M^+, 56), 117 (100), 115 (42), 91 (40), 78 (9), 65 (11), 51 (9).

(2*E*)–but–2–en–1–ylbenzene (*E*)-4g: minor product. MS (70 eV, EI): *m*/*z* (%) = 132 (M^+, 51), 117 (100), 115 (44), 104 (4), 91 (37), 77 (12), 65 (13), 51 (12).

(2*Z*)–oct–2–ene (*Z*)-4h: major product. MS (70 eV, EI): *m*/*z* (%) = 112 (M^+, 49), 83 (26), 70 (56), 55 (100).

(2*E*)–oct–2–ene (*E*)-4h: minor product. MS (70 eV, EI): *m*/*z* (%) = 112 (M^+, 32), 83 (19), 70 (45), 55 (100).

(2*Z*)–1,3–diphenylprop–2–en–1–one (*Z*)-8a: minor product. MS (70 eV, EI): *m*/*z* (%) = 208 (M^+, 40), 207 (100), 193 (16), 177 (7), 165 (8), 131 (13), 103 (17), 77 (22), 51 (9).

(2*E*)–1,3–diphenylprop–2–en–1–one (*Z*)-8a: major product. MS (70 eV, EI): *m*/*z* (%) = 208 (M^+, 60), 207 (100), 191 (4), 179 (19), 165 (10), 131 (28), 103 (25), 77 (55), 51 (18).

(2*Z*)–3–(2–methylphenyl)–1–phenylprop–2–en–1–one (*Z*)-8b: minor product. MS (70 eV, EI): *m*/*z* (%) = 222 (M^+, 56), 207 (68), 193 (39), 178 (20), 165 (16), 143 (7), 131 (15), 115 (100), 103 (39), 91 (64), 77 (21), 65 (23) 51 (16).

(2*E*)–3–(2–methylphenyl)–1–phenylprop–2–en–1–one (*E*)-8b: major product. MS (70 eV, EI): *m*/*z* (%) = 222 (M^+, 91), 204 (22), 191 (17), 178 (34), 165 (17), 145 (7), 131 (18), 115 (100), 103 (62), 91 (72), 77 (15), 65 (25) 51 (16).

(2*Z*)–3–(2–chlorolphenyl)–1–phenylprop–2–en–1–one (*Z*)-8c: minor product. MS (70 eV, EI): *m*/*z* (%) = 242 (M^+, 11), 207 (100), 178 (9), 137 (5), 105 (11), 89 (4), 77 (19), 51 (5).

(2*E*)–3–(2–chlorolphenyl)–1–phenylprop–2–en–1–one (*E*)-8c: major product. MS (70 eV, EI): *m*/*z* (%) = 242 (M^+, 1), 207 (100), 178 (7), 137 (3), 105 (7), 89 (2), 77 (15), 51 (6).

7.3.3 Variable temperature ^{31}P NMR experiments.

7.3.3.1 Case a (reaction with non-stabilized ylide 2). Typical procedure

Potassium *tert*-butylate (8.96 mg, 0.08 mmol) was added, at room temperature and under argon atmosphere, to a mixture of triphenylethyl phosphonium bromide (**1**, 30 mg, 0.08 mmol) in dry THF (2 mL). When the colour of the mixture became orange indicating the formation of the ylide **2**, the mixture was transferred into an NMR spectroscopy tube and cooled at –78 °C. The ^{31}P NMR spectrum of the ylide was recorded at this temperature (δ = 15.1 ppm), then 1 eq. of **3a** was quickly added and the ^{31}P NMR spectrum of the reaction mixture was recorded. Two new signals appeared in the spectrum, at –60.6 ppm (*cis*-oxaphosphetane), and –60.7 ppm (*trans*-oxaphosphetane) that integrated 9/91, respectively. On gradually warming the temperature of the probe until +25 °C, the oxaphosphetane and ylide peaks gradually disappeared, and a new singlet arose at +29.3 ppm (it began to appear at about –30 °C) due to the formation of triphenylphosphine oxide. The GC-MS analysis of the final reaction mixture showed presence of the *E*-**4a** /*Z*-**4a** olefins in 18/82 relative ratio, as reported in Table 1.

7.3.3.2 Case b (reaction with stabilized ylide 7). Typical procedure:

tert-butylate (8.96 mg, 0.08 mmol) was added, at room temperature and under argon atmosphere, to a mixture of phenacyltriphenylphosphonium bromide (37.3 mg, 0.08 mmol) in dry THF (2 mL). When the colour of the mixture became orange indicating the formation of the ylide. The mixture was transferred into an NMR spectroscopy tube and cooled at –100 °C. The ^{31}P NMR spectrum of the ylide **7** was recorded at this temperature (17.0 ppm) then 1 eq. of **3a** was quickly added and the ^{31}P NMR spectrum of the reaction mixture was recorded but in this case no signals in the pentacoordinate phosphorus intermediate region were detected. On gradually warming the temperature of the probe until +25 °C, the ylide peak gradually disappeared, and a new singlet arose at 29.3 ppm (it appeared at about –30 °C) due to the formation of triphenylphosphine oxide. No intermediates were detected also when the reaction course was monitored at 0 °C and at 25 °C. The GC-MS analysis of the final reaction mixture showed presence of *E*-**8a** /*Z*-**8a** olefins in 96/4 relative ratio.

7.4 References

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Chapter 8

ROLE OF THE HEXACOORDINATION OF PHOSPHORUS: SYNTHESIS OF ASYMMETRIC PHOSPHINES[1]

8.1 Introduction

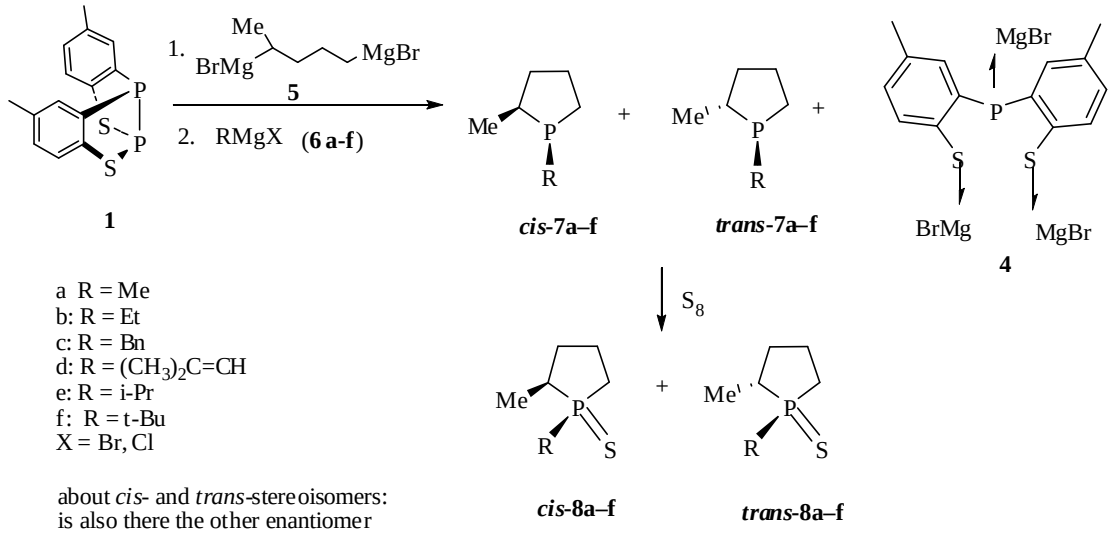
Up to now, many studies have reported that the outcome of the reactions involving phosphorus is governed by the formation of pentacoordinate intermediates. The ability of molecule **1** to stabilize also hypercoordinated phosphorus intermediates prompted us to verify whether hexacoordinate phosphorus intermediates also play a role in determining the stereochemical outcome of reactions involving phosphorus species.

For this purpose, we decided to study what happens when an unsymmetrical bis-Grignard reagent such as 1,4-bis(bromomagnesio)pentane (**5**) is used. In this case the formation of a mixture of pentacoordinate intermediates is possible. Addition of a mono-Grignard reagent to these latter could give different hexacoordinate intermediates, resulting in different ratios of diastereomeric phospholanes such as **7**.

8.2 Results and discussion

Asymmetric tertiary phosphines **7a–f** have been obtained in different diastereomeric *cis*/*trans* ratios by reaction between benzothiadiphosphole (**1**) and the unsymmetrical bis-Grignard reagent **5**, followed by addition of a mono-Grignard reagent (**6a–f**). The phosphines ***cis*-7a–f** and ***trans*-7a–f** (each as racemic mixture) were separated as sulfides **8a–f** by adding elemental sulfur[2] to the crude reaction mixture (Scheme 8.1) and fully characterized. For the sake of simplicity only one enantiomer

of both *cis*- and *trans*- isomers is represented in Scheme 8.1, but each of them is produced as racemic mixture.



Scheme 8.1. Diastereoselective one-pot formation of phospholanes **7** and their sulfides **8**.

The reaction course was monitored by GC-MS, showing the presence, in the reaction mixture, of two compounds characterized by the same molecular ion and mass fragmentation, corresponding to the two possible, *cis*- and *trans*-, isomers. The yields and the relative diastereomeric ratios of the products are collected in Table 8.1.

Table 8.1. Reaction results

RMgX	**Product (Yield %)**[a]	**d.r. (cis/trans)**[b]
6a (R = methyl)	**8a** (60)	75 : 25
6b (R = ethyl)	**8b** (70)	70 : 30
6c (R = benzyl)	**8c** (65)	67 : 33
6d (R = 2,2-dimethylvinyl)	**8d** (35)	55 : 45
6e (R= i-propyl)	**8e** (63)	50 : 50
6f (R = t-butyl)	**8f** (62)	5 : 95

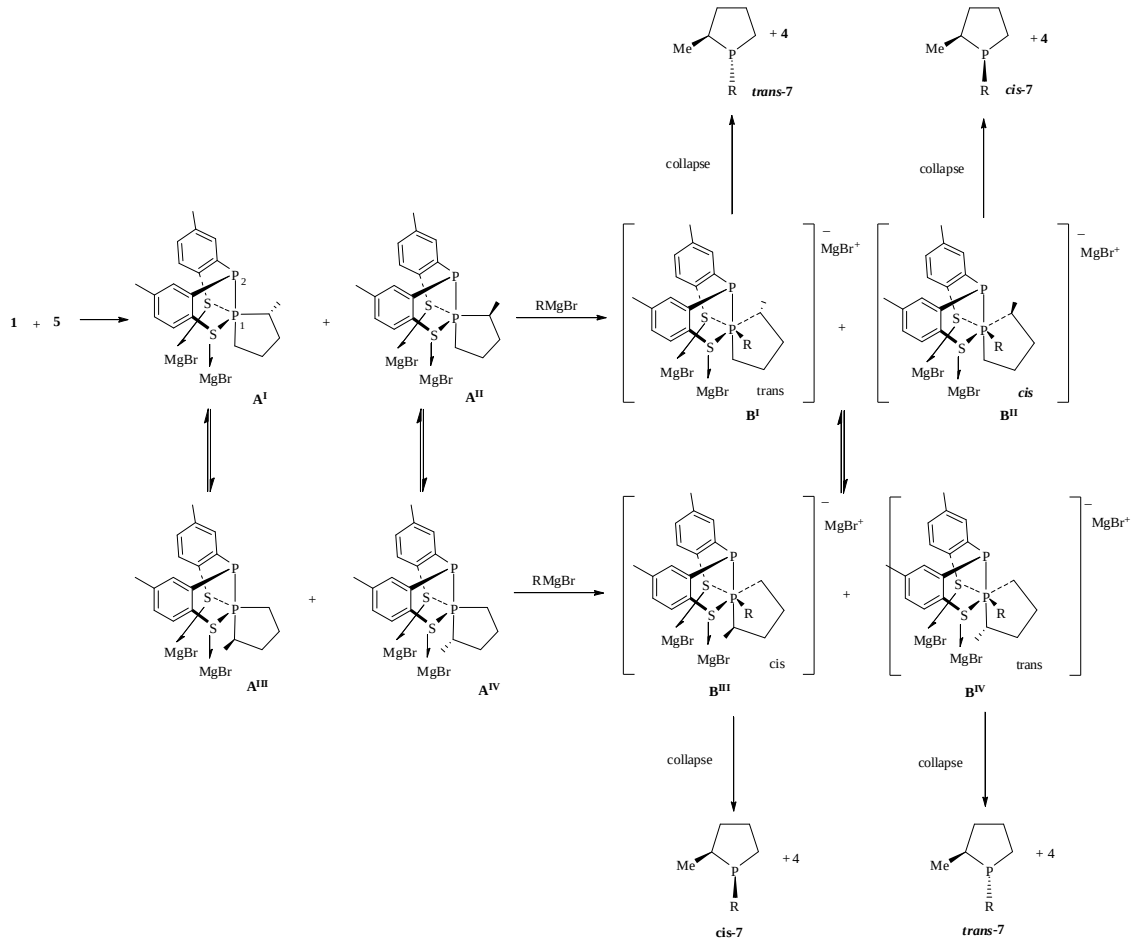
Yields and diastereomeric relative ratios of phosphine sulfides 8a–f. [a)] Yields of pure isolated sulfides. [b)] Calculated on sulfides by GC-MS.

The *cis* or *trans* configuration of each diastereoisomer was established by means of ^{1}H NOE NMR experiments on samples containing both the isomers. Because of the overlapping of many signals caused by the ^{1}H–^{31}P heteronuclear coupling, the NOE experiments were carried out under phosphorus decoupling conditions. **A** comparison between the relative GC-MS retention times and

^{31}P NMR chemical shifts of the two diastereoisomers with data obtained through NOE experiments showed that the *trans* isomer, in all cases, had both the lower retention time and the down-field ^{31}P resonance, with respect to the *cis*-isomer.

As shown in Table 8.1, the use of Grignard reagents **6a–d** gave the corresponding tertiary phosphine sulfides in *cis/trans* ratio slowly decreasing from 75/25 to 55/45 in parallel with the increase of the steric hindrance of the R group, whereas the use of a very bulky Grignard reagent, as *tert*-butylmagnesium chloride (**6f**), caused a strong enhancement of the diastereoselectivity degree, but in the opposite sense with respect to that observed in cases **a**–**d**. A border-line situation occurred using isopropyl derivative **6e**, that produced equimolar amount of *cis* and *trans* isomers.

The inversion of the diastereoselection observed on going from *n*-alkyl to more bulky Grignard reagents might be explained considering the penta- and hexa-coordinate phosphorus intermediates involved in the reaction and shown, in a simplified manner, in Scheme 8.2.



Scheme 8.2. Simplified proposed pathways to explain the diastereoselective outcome of the reaction of benzothiadiphosphole **1** with the couple bis-Grignard reagent **5** / mono-Grignard reagent.

Firstly, we take in consideration the formation of pentacoordinate intermediates. Since the bis-Grignard reagent **5** is unsymmetrical, in principle, its addition to reagent **1** can produce four possible pentacordinate intermediates $\mathbf{A^I}$–$\mathbf{A^{IV}}$, whose relative stereochemical relationships are as follows: intermediates $\mathbf{A^I}$ and A^{II} are enantiomeric forms, as well as $\mathbf{A^{III}}$ and $\mathbf{A^{IV}}$, while $\mathbf{A^I}$ and $\mathbf{A^{III}}$, as well as $\mathbf{A^{II}}$ and $\mathbf{A^{IV}}$, can be converted into one another through pseudorotation (TR or Berry) processes.[3,4]

Since there is an intramolecular overcrowding in trigonal-bipyramidal structures[5] the steric factors will have a considerable influence on the stability of such intermediates. In particular, one can state that $\mathbf{A^I}$ and $\mathbf{A^{II}}$ will be more favoured than $\mathbf{A^{III}}$ and $\mathbf{A^{IV}}$, respectively, because in structures $\mathbf{A^I}$ and $\mathbf{A^{II}}$ the methyl substituent of the phospholane ring is bonded to the carbon atom arranged in the less sterically hindered equatorial position. As previously reported for the reaction between **1** and symmetrical bis-Grignard reagents,[5] also in present case pentacoordinate species $\mathbf{A^I}$–$\mathbf{A^{IV}}$ are stabilized by the presence of three cycles around one phosphorus atom. This increases the life-time of these species permitting us to detect them and to follow the reaction course through ^{31}P NMR spectroscopy. However, the interconversion rate of these isomers give rise to only one averaged signal as two doublets at δ= –10.7 ($^1J_{P\text{-}P}$ = 196 Hz) and δ= –44.4 ($^1J_{P\text{-}P}$ = 196 Hz) ppm.

Nevertheless, the relative stability of pentacoordinate intermediates $\mathbf{A^I}$–$\mathbf{A^{IV}}$ is not the factor responsible for the stereochemical outcome of our reactions, since in these pentacoordinate intermediates the substituent derived from the addition of the mono-Grignard reagent (which drives the diastereoselectivity observed) is not yet present.

An explanation of the results shown in Table 781 can only be made by considering the fate of these intermediates when the mono-Grignard reagent is added to them. The nucleophilic attack of the mono-Grignard reagent on the pentacoordinate phosphorus atom of intermediates $\mathbf{A^I}$–$\mathbf{A^{IV}}$ can generate four hexacoordinated diastereomeric forms $\mathbf{B^I}$–$\mathbf{B^{IV}}$, each together with its own enantiomeric form: these latter species, for sake of simplicity, are neither shown in Scheme 8.3, nor considered in the following discussion. In intermediates $\mathbf{B^I}$ and $\mathbf{B^{IV}}$ the methyl substituent on the phospholane ring and the R group on the hypercoordinate phosphorus atom are in *trans* relationship, while in $\mathbf{B^{II}}$ and $\mathbf{B^{III}}$ they are in *cis* relative position and one can evince that *trans*-forms are less hindered, and thus more stable, than *cis* ones. Hexacoordinate intermediates **B** spontaneously collapse, as already reported,[6] giving racemic mixtures of *trans*- and *cis*-phospholanes in relative ratio depending on the mono-Grignard reagent added to pentacoordinate precursor.

The possibility that one of the five-membered rings containing P-S bond in $\mathbf{A^{I–IV}}$ is cleaved upon addition of the acyclic Grignard reagent to lead another pentacoordinate species with breakage of a P-S bond can not be completely excluded. In fact, we know that penta- and hexacoordinated species may be, in particular conditions, in equilibrium with their ionic forms and, consequently, the ^{31}P

NMR signal will be an average of the two forms. However, in the present case, we think that the amount of ionic form for B-like species (δ_{31P} ~ –60 ppm) is very low because the hexacoordinate **B** species is stabilized by the presence of the further cycle formed after addition of the bis-Grignard reagent. With these considerations in mind, it is very probable that in the case of the hexacoordinate species bearing acyclic groups previously reported in ref. 6 (δ_{31P} = –48.7 ppm), not stabilized by this further ring, the equilibrium is shifted towards the ionic form, and, consequently, its signal is shifted downfield. In this manner is explained the apparent disagreement between the two signals for the two different hexacoordinate species.

The different diastereoselectivity observed on going from case a to f can be explained as follows: in cases **a**–**d**, in which the steric hindrance of the R substituent is similar and not very high, *trans* and *cis* hexacoordinate intermediates can be formed in similar amount, but, once formed, *cis*- form, being less stable than *trans*-form, immediately collapses causing the shift of the equilibria,[7] depicted in Scheme 8.2, toward the formation of further amount of *cis*-intermediate, thus providing a final major amount of *cis*-phosphine. On the contrary, in case f, when R = *t*-Bu, the high steric hindrance of this substituent causes formation of hexacoordinate intermediates in very different relative amount, favouring *trans*- species $\mathbf{B^{I}}$ and $\mathbf{B^{IV}}$, which can not equilibrate and rapidly collapse giving almost exclusively *trans* phosphine **7f**. In the case of *i*-propyl substituent (case e), all these factors offset each other to provide equimolar amount of the two *tran*s- and *cis*- diastereomeric phosphines **7e**.

This hypothesis not only explains the experimental results, but it has been verified monitoring the reaction course by means of ^{31}P NMR spectroscopy. As shown in Figure 6.1 for case a (R=Me), chosen as example, after the addition of the bis-Grignard reagent **2** to a solution of compound 1 (Fig. 8.1, spectrum a), the ^{31}P NMR spectrum of the crude reaction mixture showed (Fig. 8.1, spectrum b) disappearance of signals of starting compound 1 and concomitant appearance of a new couple of doublets (δ= –10.7 ($^{1}J_{P\text{-}P}$ = 196 Hz) and δ= –44.4 ppm ($^{1}J_{P\text{-}P}$ = 196 Hz) in the region of pentacoordinate species A-like.[8,9]

Immediately after the addition of CH_3MgBr, appearance of new signals, in low amount, ascribed to hexacoordinate intermediates, was detected (Fig. 8.1, spectrum c), together with the signals of the diastereomeric tertiary cyclic phosphines **7a** (δ= –19.3 and –28.6 ppm) derived from the spontaneous and rapid collapse of hexacoordinate species.

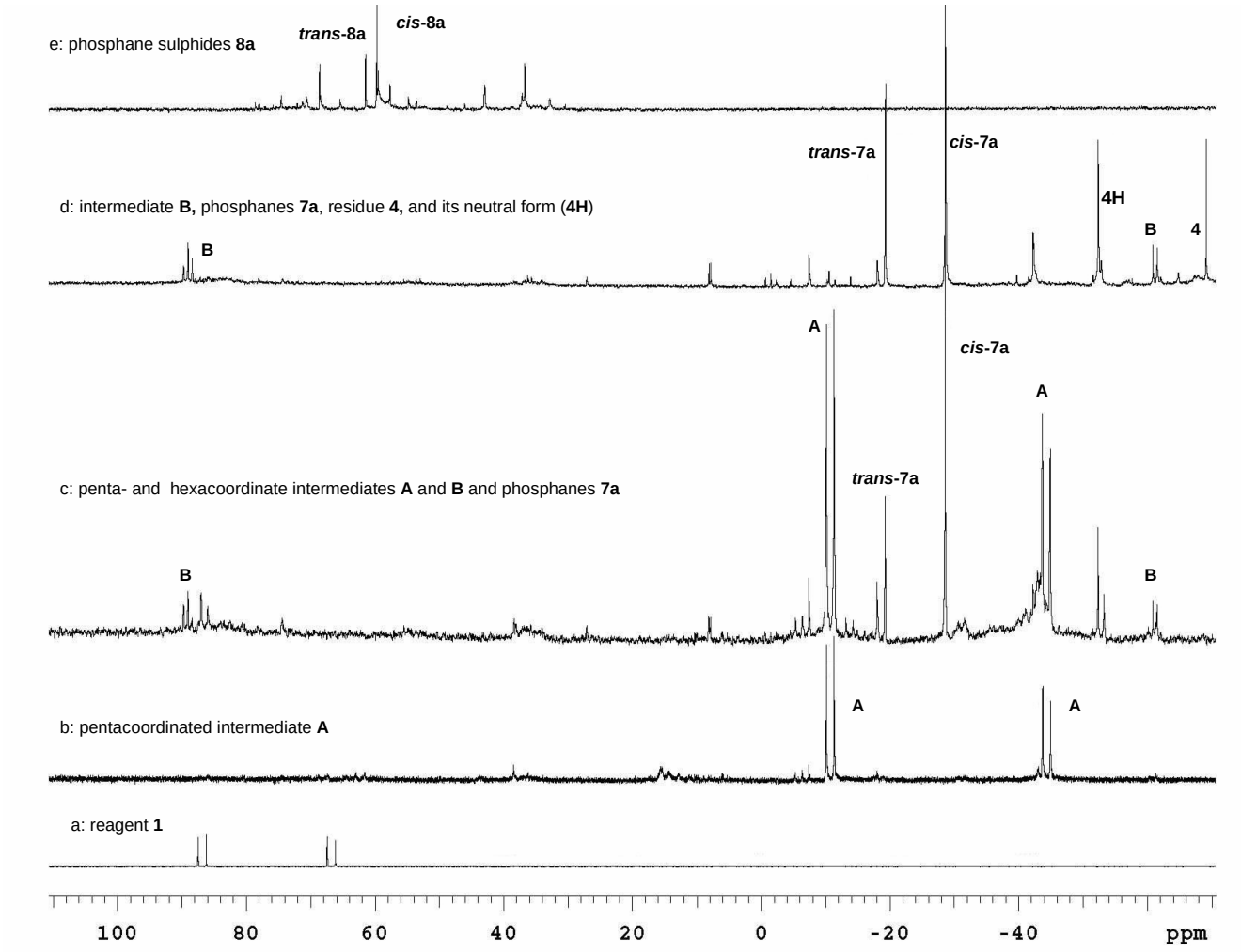


Figure 8.1. Monitoring over time the reaction course from compound **1** to phosphine sulfides **8a** through ^{31}P NMR spectroscopy of the crude reaction mixture in THF.

With time, we observed a slow decrease of signals corresponding to pentacoordinate intermediate and a concomitant gradual increase of signals belonging to the phosphines, until the situation depicted by spectrum d of Fig. 8.1, where the height of the signals ascribed to hexacoordinate intermediates, even if low, remain unmodified until the end of the reaction, with concomitant increasing of the signals of the diastereomeric phosphines **7a** (in Fig. 8.1, spectrum d shows also signals of the magnesium salt of residue of **1**, and of its neutral form (labelled as 4H). Addition of an excess of elemental sulfur to the crude final reaction mixture caused (Fig. 8.1, spectrum e) the shift of the signals of phosphines 7a toward those of the corresponding sulphides **8a**.

In case b (R = Et), the ^{31}P NMR spectrum showed two couples of doublets in the region of hexacoordinate species[10] [δ= 89.4 (d, J = 113 Hz), δ = -61.2 (d, J = 113 Hz) ppm and δ = 85.3 (d, J = 103 Hz) and δ = -57.0 (d, J = 103 Hz) ppm] which might correspond to the two most stable

diastereoisomeric forms B or, more likely, to averaged signals of *trans* (**B^{I}** and **B^{III}**) and *cis* (**B^{II}** and **B^{IV}**) species. In the case a (R = Me) only one doublet was detected (δ = 83.4 ppm (d, *J* = 115 Hz); δ = –61.2 ppm (d, *J* = 115 Hz) probably belonging to *trans*-species.

In case f, when *t*-BuMgCl was added to the solution containing the pentacoordinate specie, only one couple of doublets, in very low amount, appeared in the ^{31}P NMR spectrum, together with the signals of tertiary phosphines **7f** (with a huge excess of the signal belonging to ***trans*-7f**) and of compound **4**. Probably, in this case the signal of the hexacoordinate intermediate precursor of *cis*-phosphine is present in amount so small as not to be detectable. In all cases, after addition of elemental sulfur to the final reaction mixture, ^{31}P NMR spectrum showed mainly signals related to *cis*/*trans* phosphine sulfides **8**.

8.3 Experimental section

8.3.1 General

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at 400, 100.56 and 161.89 MHz, respectively. Phosphorus decoupled ^{1}H NOE NMR spectra were recorded at 600 MHz. Chemical shifts are referenced to TMS for ^{1}H NMR in $CDCl_3$, to the solvent for 13C NMR (δ =77.0 ppm for $CDCl_3$) and to external standard 85% H_3PO_4 for ^{31}P NMR. *J* values are given in Hz. GC-MS analyses were performed on an gas chromatograph equipped with a (5%-phenyl)-methylpolysiloxane column (30 m. length, 0.250 mm. i.d., 0.25μm thickness), interfaced to a quadrupole mass detector. Mass spectra were recorded at an ionisation voltage of 70 eV in the EI mode. All compounds **8a–f** showed characteristic IR signals at 700–732 cm-1 (P=S). THF was distilled from sodium/benzophenone ketyl, and all solvents were purified appropriately and degassed immediately prior to use. All Grignard reagents used were commercially available or prepared from bromoalkane and magnesium turnings and were titrated immediately prior to use by standard methods. Air- and moisture-sensitive solutions and reagents were handled in dried apparatus under dry argon using standard Schlenk-type techniques.

8.3.2 Synthesis for tertiary cyclic phosphine sulphides. General procedure

Bis-Grignard reagent 5 (0.333 mmol), prepared from the corresponding bromide and magnesium turnings, was added to a solution of benzothiadiphosphole **1** (0.102 g, 0.333 mmol) in anhydrous THF (3 mL) under dry argon. After about 10 min, mono-Grignard reagent (RMgX, 0.400 mmol) was added. After about 30–40 min, sulphur (0.500 mmol) was added to obtain phosphine sulphides. After 5–10 min, the reaction mixture was treated with water. Extraction with CH_2Cl_2, treatment with anhydrous Na_2SO_4 and concentration under vacuum gave a mixture of the phosphine sulphides. Phosphine sulfides were purified by bulb-to-bulb distillation and/or by flash chromatography on silica gel column (eluent: dichloromethane).

1,2-dimethylphospholane-1-sulphide (**8a**): colorless oil, b.p.: 140–160 °C (0.1 mmHg, mixture of *cis* and *trans* isomers); ***cis*-8a**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ= 2.40–1.90 (m.s, 3H; C*H*CH_3 and CH_2P), 1.90–1.76 (m, 2H; CH_2), 1.65 (d, ^2J(H,P)=12.3 Hz, 3H; CH_3P), 1.46–1.30 (m, 1H), 1.24 (dd, ^3J(H,P)=17.3 Hz, ^3J(H,H)=7.1 Hz, 3H; C*H*$_3$CHP), 0.98–0.84 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=41.4 (d, ^1J(C,P)=54.3 Hz; CHP), 34.0 (d, ^2J(C,P)=12.2 Hz; CH_2), 33.5 (d, ^1J(C,P)=52.1 Hz; CH_2P), 23.1 (d, ^2J(C,P)=3.9 Hz; CH_2), 20.6 (d, ^1J(C,P)=53.5 Hz; CH_3P), 12.3 ppm (d, ^2J(C,P)=1.6 Hz; *C*H_3CHP); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ= 60.2 ppm (m); MS (70 eV): *m*/*z* (%): 148 (M^+, 100), 133 (32), 120 (41), 115 (29), 106 (30), 94 (14), 78 (34), 63 (47). ***trans*-8a**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ= 2.40–1.90 (m.s, 3H; C*H*CH_3 and CH_2P), 1.90–1.76 (m, 2H; CH_2), 1.77 (d, ^2J(H,P)=12.6 Hz, 3H; CH_3P), 1.46–1.30 (m, 1H), 1.25 (dd, ^3J(H,P)=17.7 Hz, ^3J(H,H)=6.9 Hz, 3H; C*H*$_3$CHP), 0.98–0.84 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=35.5 (d, ^1J(C,P)=50.1 Hz; CHP), 34.8 (d, ^1J(C,P)=51.3 Hz; CH_2P), 32.7 (d, ^2J(C,P)=14.9 Hz; CH_2), 22.3 (d, ^2J(C,P)=3.1 Hz; CH_2), 21.5 (d, ^1J(C,P)=47.5 Hz; CH_3P), 14.1 ppm (s; *C*H_3CHP); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=61.9 ppm (m); MS (70 eV): *m*/*z* (%):148 (M^+, 100), 133 (28), 120 (39), 115 (15), 106 (50), 94 (19), 78 (48), 63 (42). Elemental analysis calcd (%) for $C_6H_{13}PS$: C 48.62, H 8.84; found: C 48.44, H 8.81.

1-ethyl-2-methylphospholane-1-sulphide (**8b**): colorless oil, b.p.: 145–155 °C (0.1 mmHg, mixture of *cis* and *trans* isomers); ***cis*-8b**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ= 2.50–1.60 (m.s, 7H; CH and CH_2), 1.60–1.23 (m, 4H), 1.35 (dd, ^3J(H,P)=16.3 Hz, ^3J(H,H)=7.4 Hz, 3H; C*H*$_3$CHP), 1.09–0.50 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=42.0 (d, ^1J(C,P)=51.5 Hz; CH), 34.3 (d, ^2J(C,P)=10.9 Hz; CH_2), 31.5 (d, ^1J(C,P)=50.3 Hz; CH_2), 23.1 (d, ^2J(C,P)=3.4 Hz; CH_2), 22.1 (d, ^1J(C,P)=45.7 Hz; CH_2), 12.4 (d, ^2J(C,P)=1.6 Hz; *C*H_3CHP), 6.4 ppm (d, ^2J(C,P)=4.7 Hz; *C*H_3CH_2P);

^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=68.7 ppm (m); MS (70 eV): 162 (M^+, 93), 134 (100), 119 (11), 106 (19), 100 (14), 92 (26), 63 (35). ***trans*-8b**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ=2.50–1.60 (m.s, 7H; CH and CH_2), 1.60–1.38 (m, 4H), 1.40 (dd, ^3J(H,P)=17.5 Hz, ^3J(H,H)=7.6 Hz, 3H; CH_3CHP), 1.09–0.50 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=36.6 (d, J= 9.9 Hz; CH_2), 33.7 (d, ^1J(C,P)=51.0 Hz; CH), 33.0 (d, ^1J(C,P)=50.9 Hz; CH_2), 26.9 (d, ^1J(C,P)=48.3 Hz; CH_2), 23.4 (d, ^2J(C,P)=4.3 Hz; CH_2), 14.4 (s, CH_3), 6.9 ppm (d, ^2J(C,P)=4.3 Hz; CH_3CH_2P), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=71.6 ppm (m); MS (70 eV): *m*/*z* (%): 162 (M^+, 84), 134 (100), 119 (10), 106 (15), 100 (12), 92 (35), 63 (36). Elemental analysis calcd (%) for $C_7H_{15}PS$: C 51.82, H 9.32; found: C 51.90, H 9.35.

1-benzyl-2-methylphospholane-1-sulphide (**8c**): colorless oil, b.p.: 145–165 °C (0.1 mmHg, mixture of *cis* and *trans* isomers); ***cis*-8c**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ= 7.37–7.25 (m.s, 5H; Ph), 3.20 (dd, J=14.4 Hz, J=14.4 Hz, 1H; CH_2Ph), 3.11 (dd, J=13.7 Hz, J=8.9 Hz, 1H; CH_2Ph), 2.44–0.82 ppm (m.s, 7H), 1.32 ppm (dd, ^3J=16.1 Hz, ^3J=6.9 Hz, 3H; CH_3CHP); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=131.5 (d, J(C,P)=7.9 Hz; C), 130.4 (d, J(C,P)=4.8 Hz; CH), 128.8 (d, J(C,P)=2.4 Hz; CH), 127.5 (d, J(C,P)=3.2 Hz; CH), 42.8 (d, ^1J(C,P)= 50.9 Hz; CH), 37.6 (d, ^1J(C,P)=39.2 Hz; CH_2), 34.2 (d, ^2J(C,P)= 10.4 Hz; CH_2), 30.5 (d, ^1J(C,P)=50.6 Hz; CH_2), 23.0 (d, ^2J(C,P)=4.7 Hz; CH_2), 12.4 ppm (d, ^2J(C,P)=1.6 Hz; CH_3); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4) δ=65.6 ppm (m); MS (70 eV): *m*/*z* (%): 224 (M^+, 93), 133 (99), 91 (100), 63 (30). ***trans*-8c**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ=7.38–7.25 (m.s, 5H; Ph), 3.36 (d, J=13.7 Hz, 2H; CH_2Ph), 2.44–0.82 ppm (m.s, 7H), 1.14 ppm (dd, ^3J=17.6 Hz, ^3J=6.9 Hz, 3H; CH_3CHP); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=132.1 (d, J(C,P)=7.9 Hz; C), 129.9 (d, J(C,P)=4.8 Hz; CH), 128.9 (d, J(C,P)=3.3 Hz; CH), 127.6 (d, J(C,P)=3.3 Hz; CH), 42.2 (d, ^1J(C,P)=41.0 Hz; CH_2), 34.4 (d, ^2J(C,P)=10.4 Hz; CH_2), 33.3 (d, ^1J(C,P)=51.7 Hz; CH_2), 33.1 (d, ^1J(C,P)=50.6 Hz; CH), 23.6 (d, ^2J(C,P)=4.4 Hz; CH_2), 14.2 ppm (CH_3); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=68.1 ppm (m); MS (70 eV): *m*/*z* (%): 224 (M^+, 81), 133 (94), 91 (100), 63 (27). Elemental analysis calcd (%) for $C_{12}H_{17}PS$: C 64.26, H 7.64; found: C 64.14, H 7.67.

2-methyl-1-(2-methylprop-1-en-1-yl)phospholane 1-sulphide (**8d**): colorless oil, mixture of *cis* and *trans* isomers; ***cis*-8d**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ= 5.62 (d, ^2J(H,P)=24.0 Hz; =CHP), 2.60–1.86 (m, 3H; CH and CH_2), 2.30 (dd, J=2.5 Hz, J=1.0 Hz, 3H; CH_3CH=), 1.91 (dd, J=1.1 Hz, J=1.1 Hz, 3H; CH_3CH=), 1.70–1.58 (m, 2H), 1.48–1.24 (m, 1H), 1.29 (dd, ^2J(H,P)=18.0 Hz, ^3J(H,H)=6.3 Hz, 3H; CH_3CHP), 1.00–0.78 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) δ=133.3 (d, ^2J(C,P)=10.5 Hz; $(CH_3)_2C$=), 114.6 (d, ^1J(C,P)=72.3 Hz; C=*C*HP), 43.8 (d, ^1J(C,P)=55.2

Hz; CHP), 35.7 (d, ^{1}J(C,P)=55.1 Hz; CH_2), 34.1 (d, ^{2}J(C,P)=10.3 Hz; CH_2), 28.8 (d, ^{3}J(C,P)=16.2 Hz; *C*H_3C=CHP), 23.4 (d, ^{2}J(C,P)=4.6 Hz; CH_2), 22.0 (d, ^{3}J(C,P)=7.9 Hz; *C*H_3=CHP), 13.1 ppm (d, ^{2}J(C,P)=1.7 Hz; *C*H_3CHP); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=51.4 ppm (m); MS (70 eV): *m*/*z* (%): 188 (M^+, 100), 173 (11), 155 (15), 133 (31), 117 (9), 99 (21), 86 (21), 63 (36). ***trans*-8d**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ=5.53 (d, ^{2}J(H,P)=24.4 Hz; =CHP), 2.58–1.84 (m, 3H; CH and CH_2), 2.20 (dd, *J*=2.4 Hz, *J*=1.1 Hz, 3H; C*H*$_3$CH=), 1.95 (dd, *J*=1.2 Hz, *J*=1.2 Hz, 3H; C*H*$_3$CH=), 1.70–1.56 (m, 2H), 1.46–1.22 (m, 1H), 1.23 (dd, ^{2}J(H,P)=16.8 Hz, ^{3}J(H,H)=6.7 Hz, 3H; C*H*$_3$CHP), 1.02–0.76 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): *δ*=133.4 (d, ^{2}J(C,P)=11.0 Hz; $(CH_3)_2$*C*H=), 120.5 (d, ^{1}J(C,P)=73.6 Hz; C=*C*HP), 36.7 (d, ^{1}J(C,P)=54.9 Hz; CH_2), 36.6 (d, ^{1}J(C,P)=54.6 Hz; CH), 34.3 (d, ^{2}J(C,P)=10.0 Hz; CH_2), 28.2 (d, ^{3}J(C,P)=16.2 Hz; *C*H_3=CHP), 23.0 (d, ^{2}J(C,P)=4.0 Hz; CH_2), 21.9 (d, ^{3}J(C,P)=8.0 Hz; *C*H_3=CHP), 14.2 ppm (s, *C*H_3CHP); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=53.9 ppm (m); MS (70 eV): *m*/*z* (%): 188 (M^+, 100), 173 (11), 155 (12), 133 (29), 119 (9), 99 (12), 86 (14), 63 (33). Elemental analysis calcd (%) for $C_9H_{17}PS$: C 57.42, H 9.10; found: C 57.21, H 9.13.

1-isopropyl-2-methylphospholane-1-sulphide (**8e**): colorless oil, b.p.: 145–165 °C (0.1 mmHg, 1:1 mixture of *cis* and *trans* isomers); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ= 2.40–2.20 (m, 2H), 2.16–1.85 (m, 4H), 1.70–1.33 (m, 2H), 1.32–1.15 ppm (m, 9H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) *δ*=42.9 (d, ^{1}J(C,P)=49.0 Hz; CH), 34.9 (d, ^{2}J(C,P)=5.5 Hz; CH_2), 34.8 (d, ^{2}J(C,P)=5.0 Hz; CH_2), 32.8 (d, ^{1}J(C,P)=49.9 Hz; CH), 32.4 (d, ^{1}J(C,P)=49.9 Hz; CH_2), 31.0 (d, ^{1}J(C,P)=49.5 Hz; CH_2), 30.9 (d, ^{1}J(C,P)=46.4 Hz; CH), 26.8 (d, ^{1}J(C,P)=44.6 Hz; CH), 23.7 (d, ^{2}J(C,P)=4.2 Hz; CH_2), 22.7 (d, ^{2}J(C,P)=4.0 Hz; CH_2), 17.0 (d, ^{2}J(C,P)=2.5 Hz; CH_3), 16.9 (d, ^{2}J(C,P)=1.8 Hz; CH_3), 16.5 (d, ^{2}J(C,P)=1.9 Hz; CH_3), 15.8 (d, ^{2}J(C,P)=2.4 Hz; CH_3), 14.7 (CH_3), 13.5 ppm (d, ^{2}J(C,P)=1.7 Hz; CH_3); ***cis*-8e**: ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=76.4 ppm (m); MS (70 eV): *m*/*z* (%): 176 (M^+, 59), 134 (100), 119 (11), 106 (15), 100 (14), 92 (15), 63 (26). ***trans*-8e**: ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ= 79.5 ppm (m); MS (70 eV): *m*/*z* (%): 176 (M^+, 56), 134 (100), 119 (10), 106 (13), 100 (14), 92 (15), 63 (21). Elemental analysis calcd (%) for $C_8H_{17}PS$: C 54.51, H 9.72; found: C 54.43, H 9.69.

1-*tert*-butyl-2-methylphospholane-1-sulphide (**8f**): colorless oil, b.p.: 180–200 °C (0.1 mmHg, mixture of *cis* and *trans* isomers); ***cis*-8f**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ=2.45–2.12 (m, 2H), 2.12–1.82 (m, 2H), 1.68–1.51 (m, 2H), 1.42 (dd, *J*= 15.1 Hz, *J*= 7.3 Hz, 3H), 1.31 (d, *J*= 15.5 Hz, 9H), 1.01–0.78 ppm (m, 1H); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=83.0 ppm (m); MS (70 eV): *m*/*z* (%): 190 (M^+, 39), 134 (100), 119 (10), 100 (13), 92 (30), 69 (22), 63 (31), 57

(66). ***trans*-8f** : ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ=2.50–2.40 (m, 1H), 2.22–2.13 (m, 1H), 2.14–2.00 (m, 2H), 1.93–1.53 (m, 2H), 1.26 (dd, J_1= 16.4 Hz, J_2= 7.0 Hz, 3H), 1.24 (d, *J*= 15.7 Hz, 9H), 1.01–0.78 ppm (m, 1H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C) *δ*=35.1 (d, ^{2}J(C,P)=9.0 Hz; CH_2), 33.7 (d, ^{1}J(C,P)=44.1 Hz; C), 31.3 (d, ^{1}J(C,P)=48.9 Hz; CH_2), 30.0 (d, ^{1}J(C,P)=47.6 Hz; CH), 24.9 (d, ^{2}J=(C,P)=1.5 Hz; CH_3), 24.5 (d, *J*(C,P)=3.3 Hz; CH_2), 15.0 ppm (CH_3); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C, ext. H_3PO_4): δ=86.1 ppm (m); MS (70 eV): *m*/*z* (%): 190 (M^+, 37), 134 (100), 119 (23), 92 (23), 101 (22), 64 (79), 57 (67). Elemental analysis calcd (%) for $C_9H_{19}PS$: C 56.81, H 10.06; found: C 56.87, H 10.09.

8.4 References

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3. In a turnstyle rotation (TR), permutation is postulated to occur by mutual counterrotation of a pair (one apical and one equatorial ligand) and of a trio (one apical and two equatorial ligands) with subsequent collapse to a new trigonal bipyramid. In four- and five-membered cyclic phosphoranes the ring must always play the role of the pair. The consequences of single and multiple TR processes follow from the application of the following rules. For (TR), transpose the pair ligands and rotate the trio of ligands 120° in the direction that brings the trioapical ligand into the original position of the trioequatorial ligand that remains equatorial in the isomerization. For $(TR)^2$, do not change the pair; rotate the trio as for (TR). For $(TR)^3$, transpose the pair. For a discussion of the permutational isomerization of phosphoranes by the TR process, see ref. 4b.
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Part 3

PREBIOTIC CHEMISTRY

With the term “prebiotic chemistry” we mean all reactions which could lead to the beginning of life, without the intervention of biological molecules.
We think that these reactions occur in water, in mild conditions, at room temperature (or at max 40 °C) and with simple molecules present in primordial Earth.
These reactions should have led to more complex compounds (RNA, DNA, enzymes, etc.) which have started to life.

Chapter 9

ORIGIN OF LIFE

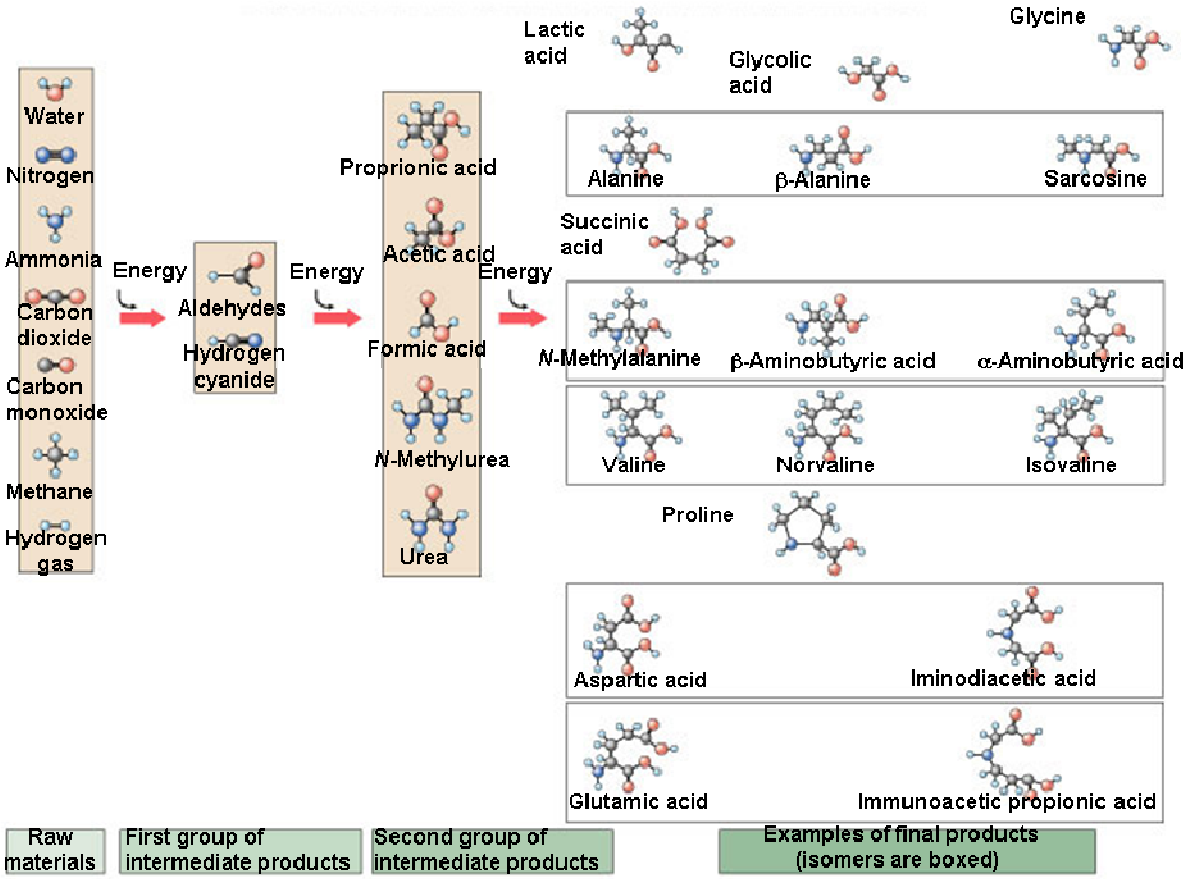
9.1 Origin of life theories

How life began on Earth is one of the great scientific mysteries. However, the question how do simple organic molecules go towards the life is largely unanswered even if there are many hypotheses. Some of these postulate the early appearance of nucleic acids ("RNA-first") whereas others postulate the evolution of simple biochemical reactions and pathways first ("metabolism-first").

There are many other theories about the origin of life.

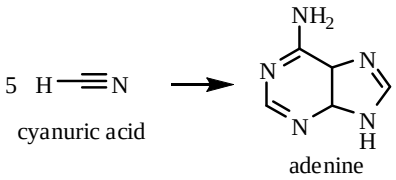
The first question, to which scientist have tried to answer, is how the first organic molecules (amino acids, sugars and other simple molecules) are originated.

Miller and Urkey[1] have conducted some experiments using a mixture of ammonia, methane, hydrogen, nitrogen, carbon's oxides and water steam, irradiating the mixture with electricity. From this experiment they obtain a complex mixture containing some molecules such amino acids, aldehydes and ureas (scheme 9.1).



Scheme 9.1 schematization of Miller-Urkey results.

Other similar experiments were conducted by Orò with cyanuric acid to obtain Adenine (scheme 9.2).



Scheme 9.2 Experiment of Orò.

The second question concerns the synthesis of polipeptides, Fox and Bada[2] have hypothesized that the poliphosphates could promote a synthesis of proteins.

Other scientists consider that origin of life could not have happened in water but on the mineral surfaces, which would function as catalyst, promoting the formation of lipidic “bubbles”, which took

place the peptide synthesys. An other similar theory, postulated by Graham Cairns-Smith, believes that the life could occur on a silicate surface (clay).[3]

All these theories belong to the metabolic approach.

The RNA-world, probably, is the most accredited theory to explain the origin of life.

In this theory the life starts after the formation of RNA molecules, which may have catalyzed the other biological reactions, as they can function as enzymes (ribozime).

Some theories believe that may have existed molecules similar to RNA but more simple, these compounds would be more stable respect to the RNA. One of these molecules is PNA[4] (figure 9.1), but many other were hypothesized (TNA, GNA, etc.), among these are also the PHA (Policyclic hydrocarbons aromatic).

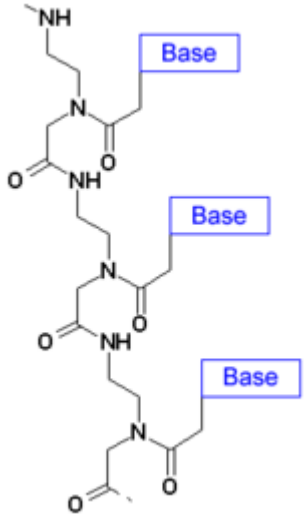


Figure 9.1 PNA fragment.

The last question is the origin of the homochirality. Intervention of ribozime could be explain the homochirality, but in the last years has evolved a new theory, hypothesized that the homochirality is due to the amino acid Serine, which forms a strong bond whit other amino acids with similar chirality.

9.2 References

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Chapter 10

THE STRANGE STABILITY OF THE PHOSPHOENOLPYRUVATE (PEP)[1]

10.1 Introduction

The chief obstacle to understand the metabolic origin of life or RNA-based life is to identify a plausible mechanism for overcoming the clutter wrought by abiotic chemistry[2]. Probably from simple abiotic and then prebiotic reactions we could arrive to simple pre-RNA molecules.

This yet unknown, but possible, "self-organized, or autocatalytic mechanism, or driver reaction"[3] might be active also in controlling the easy formation and activity of small molecules such as phosphoenolpyruvate (PEP) or others related simple phosphorus compounds and in explaining their high performance in the process of phosphorylation which is essential in the chemical evolution of life.

Most of the reactions occurring through organophosphorus intermediates are drived by the ability of the phosphorus to form "hypercoordinate" species, mainly penta- and hexa-coordinate,[4,5] which are fluxional species because they may undergo positional changes among substituents. For example, phosphoryl transfer reactions, which are basic biological processes, are generally assumed to involve pentacoordinated intermediates, that influence the outcome of the reactions.[6] The trigonal bipyramidal geometry (TBP) represents the most common structure of pentacoordinated phosphorus intermediates.

Sufficiently long-lived pentacoordinated intermediates can undergo stereomutation or positional interchange of the substituents at pentacoordinated phosphorus by a Turnstile rotation[7] (TR) or a resultwise equivalent Berry pseudorotation[8] (BPR) that are very rapid processes, since the energy barriers of pseudorotation are usually relatively low.[9] The relative position of the substituents in pentacoordinated compounds depends on their steric hindrance and apicophilicity. Apicophilicity is the relative preference of substituents to occupy the apical positions as opposed to the equatorial

positions in trigonal bipyramidal (TBP) structures: a number of experimental results and theoretical calculations have indicated a general propensity of the more electronegative substituents to prefer the apical positions; in addition, bulky ligands prefer the equatorial positions.[10] Their stability strongly depends from their structure; in particular, when it is possible, the formation of a cycle around the pentacoordinate phosphorus atom is favored over that of the corresponding acyclic intermediate by a factor of 10^6–10^8, as reported by Westheimer.[11] In this way any other possible collateral reaction in which the phosphorus atom belongs to an acyclic pentacoordinate intermediate is practically minimized or annulled.

From these considerations it can be deduced that the super-activated formation of cyclic pentacoordinate phosphorus intermediates might be a possible candidate for this hypothesized important "self-organized or autocatalytic mechanism" acting either on simple molecules or on complex molecules in processes in which phosphorylation or dephosphorylation reactions are involved, processes which are the centerpiece for the evolution of life. In fact, strongly activated phosphorylation processes involving small molecules as the so-called "high-energy" biomolecules (*e.g.* PEP) might be explained postulating the very favored formation of cyclic pentacoordinate phosphorus intermediates.[6,12,13]

We have study the hydrolysis of PEP to explain why PEP is a very powerful phosphorylating agent for alcohol moiety in metabolic processes but is very stable in water and to see if the mechanism found for PEP may be applied also to the non-enzymatic cleavage or elongation of RNA molecules.

PEP is a simple three-carbon molecule, containing a phosphoryl group, that occupies a central role in primary metabolism, it is a very strong phosphorylating agent, permitting a wide range of metabolic events.[14] It might be one of the first prebiotic molecules originating probably from glucose in an aqueous puddle of the primitive Earth.[15]

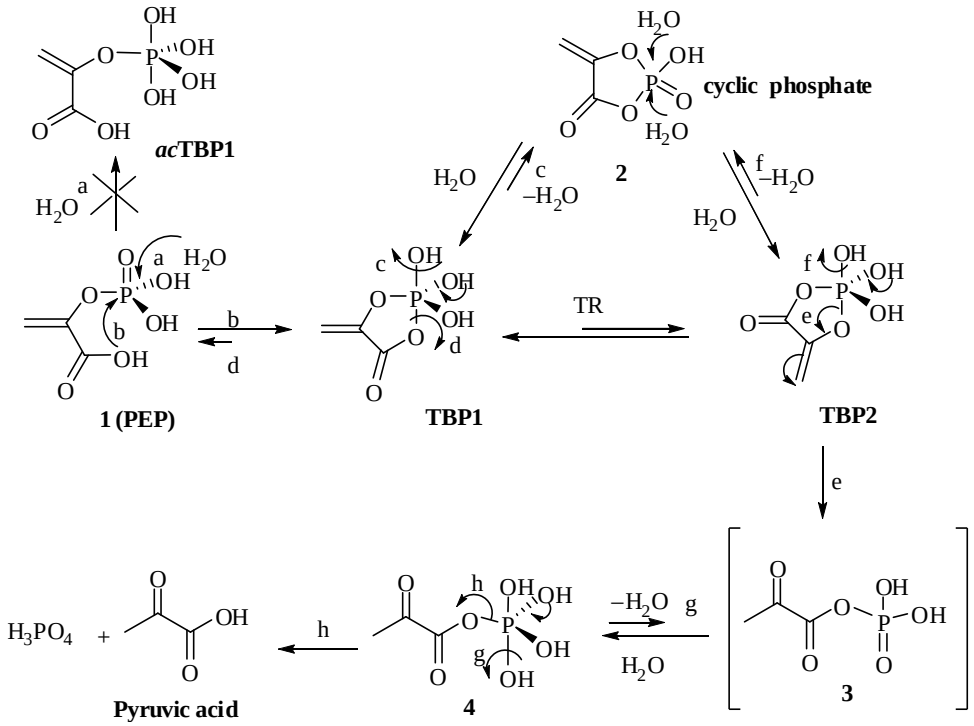
PEP is a compound very stable in aqueous solution. In fact, the non-enzymatic hydrolysis of PEP occurs at high temperature (60–75 °C), while the hydrolytic rate is enhanced at room temperature only in the presence of several metal ions.[16] In contrast, when PEP is in the presence of alcohol it is very unstable and immediately the formation of phosphorylation products occurs. What is the reason of these contrasting behaviours?

Benkovic[17] studied the non-enzymatic hydrolysis of PEP and postulated a mechanism in which the cyclic phosphate **2** (Scheme 9.1), isolated by Kirby,[18] is involved as intermediate. Consequently, they supposed the formation of a cyclic pentacoordinate phosphorus intermediate or transition state as precursor of the cyclic phosphate **2**.

10.2 Results and discussion

10.2.1 Hydrolysis of PEP

We have reinvestigated this non-enzymatic hydrolysis of PEP by following the course of the reaction by ^{31}P NMR spectroscopy. On the basis of our spectroscopic studies, reported below, and on the basis of the large number of studies that now exist concerning cyclic hypervalent phosphorus intermediates[6,19] we have drawn a mechanism which give a clear explanation of the contrasting behaviour of PEP. In other words, we will explain why PEP is very resistant to hydrolysis while it is, in apparent contrast, a powerful phosphorylating agent of alcohols (*e.g.* it easily undergoes addition of methanol). This phenomenon can be explained as shown in Scheme 10.1.



Scheme 10.1. Mechanism of non-enzymatic hydrolysis of PEP. When dissolved in water (neutral conditions) at room temperature PEP (**1**) exists prevalently in the cyclic form **TBP1**, stable at least for four months. In acidic (pH~2) aqueous solution **1** is completely hydrolyzed giving H_3PO_4 and pyruvic acid in about three months. In acidic (pH~2) aqueous solution and at 60 °C **1** is completely hydrolyzed after 6 hours. Intermediate **2** is very important in this process.

An intramolecular nucleophilic attack, *via b*, by the hydroxyl oxygen atom of the carboxy group to the P=O group of PEP (**1**) could form a cyclic pentacoordinate phosphorus intermediate such as **TBP1** which is more stable of a factor of about $10^{6\text{-}8}$ with respect to the corresponding acyclic

pentacoordinate intermediate ***ac*TBP1** derived by the attack of water, *via a*, on the same P=O group (Scheme 1). As a consequence of this huge rate difference between intra- and intermolecular pathways *a* and *b*, water cannot attack P=O group of PEP and this explains the great stability of PEP in water. Decomposition of **TBP1**, *via c*, by elimination of water, gives, in very small amount, the cyclic phosphate intermediate **2**. Addition of water to **2** could give again intermediate **TBP1** together with **TBP2**. Permutational isomerization of **TBP1** might also give the pentacoordinate intermediate **TBP2**. On the other hand, since the more electron-acceptor group tends to prefer the apical positions, the formation of the intermediate **TBP2** is very disfavoured with respect to that of **TBP1** (in fact, the PO-C=O group, in apical position in **TBP1**, is more apicophilic than the PO-C=C– group, in apical position in **TBP2**).

Then, decomposition of the intermediate **TBP2**, *via e,* gives pyruvoyl dihydrogen phosphate (**3**) which now can undergo easily an attack by water. In this manner is formed pentacoordinate phosphorus compound 1-oxo-1-[(tetrahydroxyphosphoranyl)oxy]acetone (**4**), which immediately collapses to pyruvic acid and phosphoric acid. From Scheme 10.1 it is evident that hydrolysis comes only from the intermediate **TBP2** derived principally from **2**. A small portion of **TBP2** could derive from **TBP1** but this process might be very disfavoured in normal reaction conditions (room temperature and absence of metal ions) where **TBP1** is presumably largely favoured over **TBP2** because the PO-C=O group is more apicophilic than the PO-C=C- group.

With these considerations in mind, we carried out hydrolysis of PEP in different experimental conditions and the reaction course was followed through ^{31}P NMR spectroscopy.

When PEP was dissolved at room temperature in neutral aqueous solution we noted only the formation of an intermediate which spectroscopic data are (Figure 10.1) in agreement with structure **TBP1** (Scheme 10.1).

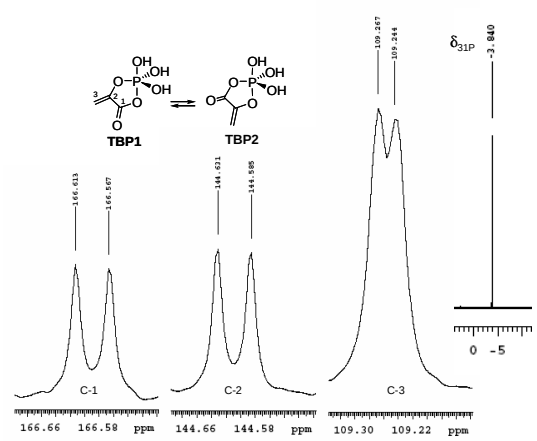


Figure 10.1. Expanded views of ^{31}P NMR (right, δ_{31P} = –3.8 ppm) and ^{13}C NMR spectra of PEP dissolved in D_2O: δ_{13C} = 166.6 (d, *J*= 6.9 Hz), 144.6 (d, *J*= 7.1 Hz), 109.2 ppm (d, *J*= 3.8 Hz).

This compound gives a signal, in ^{31}P NMR spectrum, at δ_{31P} = –3.8 ppm. It is stable also after several months and not intermediates as **2**, **TBP2**, **4**, neither trace of phosphoric acid are found also after four months. It should be noted that the ^{31}P NMR chemical shift of PEP in water it has been reported[19] to be δ= – 3.61 ppm, in agreement with our findings.

The hypothesis that PEP in aqueous solution is in a cyclic form, and consequently with the phosphorus atom in a pentacoordinate state, was confirmed by ^{13}C NMR analysis (Figure 10.1). The obtained spectral data: δ_{13C} = 166.6 (d, *J*= 6.9 Hz), 144.6 (d, *J*= 7.1 Hz), 109.2 ppm (d, *J*= 3.8 Hz) are consistent with a cyclic structure for **TBP1**. Particularly diagnostic are the very close values of the two coupling constants of the signals belonging to the carboxyl carbon atom (C-1) and to the vinylic carbon atom (C-2) that indicate that they are members of a cyclic structure. In fact, in the acyclic structure **1**, these coupling constant values can not expected to be so similar, because vinylic carbon atom is characterized by a $^{2}J_{P\text{-}C}$ coupling constant, while for the carboxyl carbon atom a smaller $^{3}J_{P\text{-}C}$ must be found. These considerations are supported also by the fact that similar values of $^{2}J_{P\text{-}C}$ coupling constant were found for the cyclic compound **2**, prepared as reported in literature.[19] These data demonstrate that PEP in aqueous solution is very stable and, surprisingly, it is prevalently in a cyclic form in which its phosphorus atom is pentacoordinate, as well described by the structure of **TBP1**. It should be noted that X-Ray diffraction analysis of PEP in solid state revealed that it is an acyclic compound.[21]

When the hydrolysis of PEP was carried out in acidic conditions (pH~2), at room temperature, we observed again the immediate formation of **TBP1** but also the slow formation of the final product of hydrolysis (phosphoric acid, δ_{31P} = 0.5 ppm). The reaction reached the end point after about three months.

Furthermore, when this reaction was carried out at 60 °C, after one hour we observed again a high intensity signal of **TBP1**, a very small and transient signal probably belonging to compound **2** (δ_{31P} = +2.4 ppm), a low intensity signal ascribed to **4** (δ_{31P} = –10.0 ppm) and a consistent signal of phosphoric acid. At the end of the reaction, after about 6 hours, only the signal of phosphoric acid was present in the ^{31}P NMR spectrum.

10.2.2 Hydrolysis of cyclic phosphate 2

Probably, the true powerful phosphorylating agent in this mixture of intermediates is the cyclic phosphate **2**. A demonstration of this statement comes from the hydrolysis of compound **2**. In fact, when we carried out, at room temperature, the hydrolysis on pure compound **2**, synthesized by using the procedure reported by Kirby,[18] we saw (by following the reaction course through ^{31}P NMR

spectroscopy) the immediate appearance of a broad signal at δ_{31P} = –3.7 ppm, ascribed to **TBP1** and **TBP2**, probably in equilibrium. After a few minutes a sharp signal of **TBP1** (δ_{31P} = –3.8) and an high intensity signal of phosphoric acid (δ_{31P} = +0.7 ppm) together with a low intensity signal of **4**, appeared (see Scheme 10.1). When, at this point, the reaction temperature was raised until 60 °C we observed, after two additional hours, the total disappearance of **TBP1** and the total formation of phosphoric acid.

This can be explained in this manner. Addition of water to **2** is very fast because it is carried out on a phosphoryl group of a cyclic compound which is more activated of about $10^{6\text{-}8}$ fold with respect to a correspondent acyclic compound. In this case the addition of water can occur in two directions with the same probability. The one opposite to the bond PO-CO- give pentacoordinate intermediate **TBP1**, the other opposite to the bond POC=C- give pentacoordinate intermediate **TBP2**.

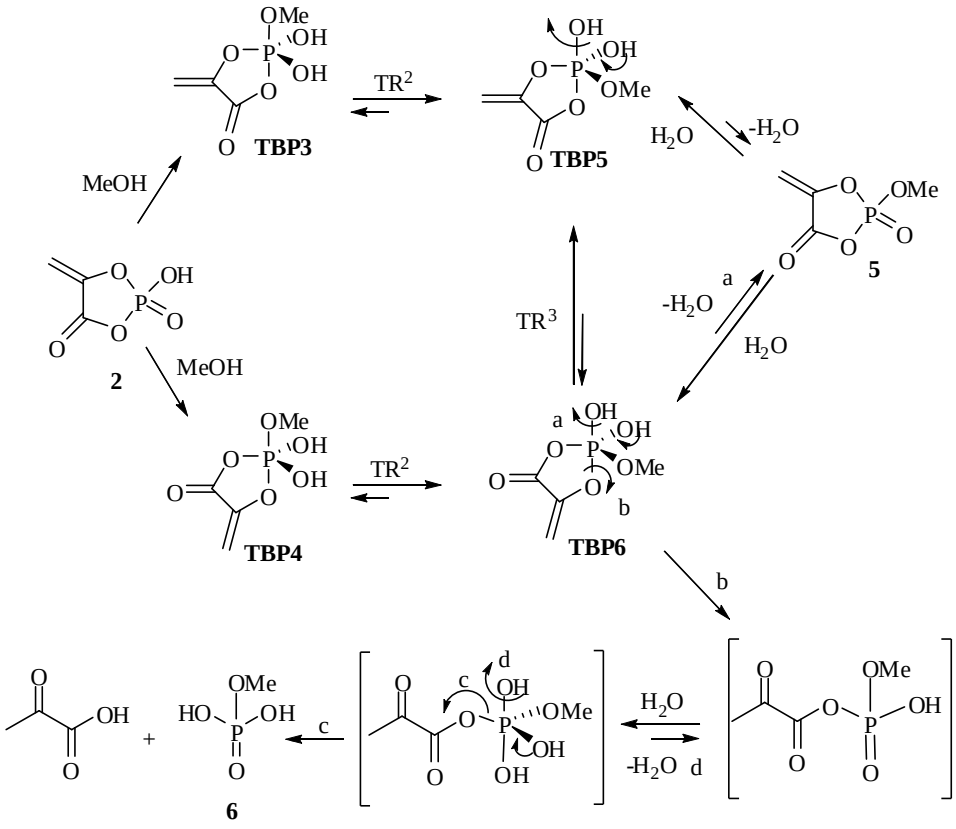
Intermediate **TBP2** which, in the first time, is the 50% of the two intermediates, immediately gives pyruvic acid and phosphoric acid probably *via* the pyruvoyl dihydrogen phosphate (**3**) and, after addition of water, *via* intermediate **4** which immediately collapses to pyruvic acid and phosphoric acid. A small part of **TBP2** might be also trasformed into its isomer **TBP1**. The intermediate **TBP1** is very stable and then it can interconvert to isomer **TBP2** or it can be transformed in compound **2** only when the reaction is carried out at 60 °C. In this manner all initial compound **2** is totally hydrolyzed after about two additional hours.

10.2.3 Addition of methanol to 2 and to PEP

Firstly we will discuss what happen during the phosphorylation of an alcohol (methanol) starting from compound **2**, then we will report the results of our study on the case of PEP.

Theoretcally, the dissolution of compound **2** in dry methanol should produce, as first intermediates, **TBP3** and **TBP4** (Scheme 10.2). But these intermediates, having in apical positions a OMe group, prefer to permutate (by TR process[7]) to the corresponding isomers **TBP5** and **TBP6** where in apical position there is an OH group which is more apicophilic than OMe. In fact, OMe is bulkier than OH. If the reaction is carried out with an alcohol larger than methanol, this preference would be greater than with methanol. In this manner, having only intermediates **TBP5** and **TBP6** in which OMe group is in equatorial position it is not possible to have elimination of MeOH with reformation of **2** (it should be remembered that in a TBP pentacoordinate intermediate the departure of a group can occur only when it is in apical positions).[22, 23] On the contrary, in the case of addition of water to **2** (above experiment, Scheme 10.1) we have always intermediate **TBP1** or **TBP2** in which it is possible to eliminate water with reformation of **2**, and for this reason the total rate of the hydrolysis is very slow.

These considerations should explain why PEP prefers to phosphorylate an alcohol rather than water.



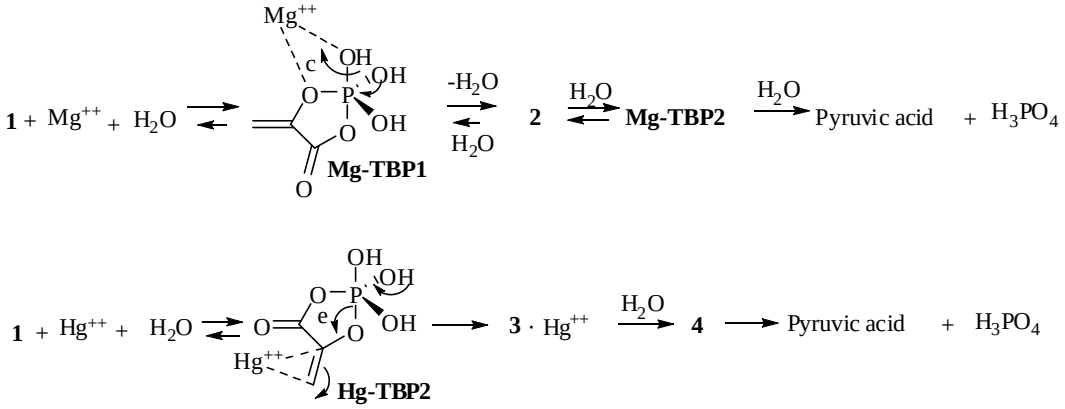
Scheme 10.2. Phosphorylation of methanol starting from pure **2**.

Experimentally we found a confirmation of this hypothesis. When compound **2** was treated with dry methanol at room temperature and the course of reaction followed by ^{31}P NMR spectroscopy we observed the immediate appearance of a signal at ^{31}P NMR (δ_{31P} = –2.6 ppm) ascribed to **TBP5** and **TBP6**, probably in rapid equilibrium, as found for **TBP1** and **TBP2** in the case of PEP. After a few minutes the formation of methyl cyclic phosphate **5** (δ_{31P} = +2.4 ppm) occurred with concomitant decrease of signal of **TBP5** and **TBP6**. After about three hours prevalent presence of **5** was detected. By addition of water to the methanolic solution of **5** we observed, after one hour, in ^{1}H and ^{31}P MMR spectra, the formation of methyl phosphate **6** (δ_{31P} = +1.5 ppm) and pyruvic acid. Subsequently, these results were confirmed when we dissolved PEP (**1**) in a solution of dry methanol at 60 °C. In this case we found similar results.

10.2.4 Hydrolysis of PEP in the presence of metal ions

When the hydrolysis of PEP is carried out in presence of some metal ions such as Mg^{++} or Hg^{++} the hydrolytic rate is enhanced. Benkovic[16] studied the catalytic activity of these metal ions on the hydrolysis of PEP *via* kinetic measurements. He found for Mg^{++} a good activity but surprisingly for Hg^{++} he found an increase of the hydrolysis rate of a factor of about 10^6, similar to that of the enzymatic hydrolysis. Now, with our knowledge about the factors which influence the apicophilicity of a group we could explain also this catalytic activity.

It is well-known[24] that mercury ion forms labile interactions with olefin bond. In analogous manner the POC=C- group in **TBP2** is coordinated with Hg^{++} and consequently this group becomes more apicophilic than PO-C=O, so stabilizing the intermediate **TBP2**. In this manner (Scheme 10.3) the equilibrium is totally shifted towards **Hg-TBP2** in which the POC=C-Hg group, owing to its high electron-withdrawing power, is the most apicophilic and thus the best leaving group. This causes the immediate apical departure of this substituent and the formation of the acyclic pyruvoyl dihydrogen phosphate (**3**) which immediately undergoes hydrolysis.



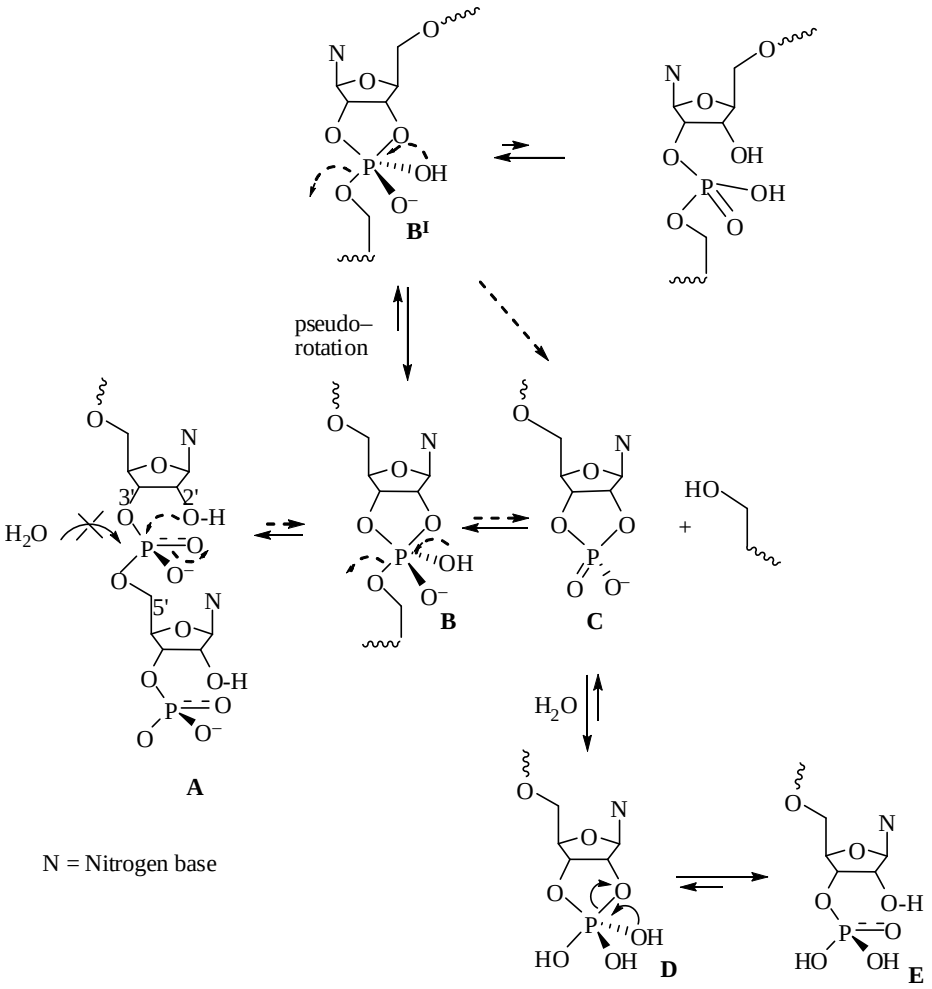
Scheme 10.3. Metal ions catalysis in PEP hydrolysis

Actually, when the hydrolysis of PEP was carried at room temperature in the presence Hg^{++} ions, and the reaction course was followed by ^{31}P NMR spectroscopy, we observed the immediate appearance of a signal at δ_{31P} = –4.1 ppm, probably belonging to **Hg-TBP2** and the concomitant appearance of the signal of phosphoric acid. The end of the reaction occurred after about 4 days at room temperature. When the same reaction was carried out at 60 °C it appeared to be complete after few minutes. When the hydrolysis of PEP was carried at room temperature in presence of Mg^{++} ions we observed, after 20 minutes, a signal at δ_{31P} = –4.3 ppm indicating the presence of a complex with Mg^{++} (**Mg-TBP1** in Scheme 9.3) together with the signal of phosphoric acid. At the end of the

reaction, after about 4 months, we observed only the signal of phosphoric acid. When this reaction was carried out at 60 °C, its end point occurred after 4 hours. Probably in this case the coordination of Mg with the two oxygen atoms, as depicted in Scheme 10.3, favors the departure of the OH group in apical position causing the formation of compound **2,** which is the true phosphorylating agent.
In all these mechanisms it has not to excluded the formation of hexacoordinated species which are probably very unstable because they have only one cycle around the P atom.[4,5] For this reason we did not detect suitable signals in the ^{31}P NMR spectrum.

10.2.5 Correlation with RNA

Now, we go to see if the mechanism found for PEP may be applied in similar manner also to the non-enzymatic cleavage (or elongation) of RNA molecules. The mechanistic details of the non-enzymatic hydrolysis of RNA remain obscure, despite extensive efforts over many years.[20,25] The emphasis of the recent investigations on RNA hydrolysis was focused on the study and the role of the factors that govern the formation, isomerisation, and breakdown of the pentacoordinated phosphorus intermediates such as **B** (Scheme 10.4) involved in this process. Now we repropose this generally accepted mechanism but on the light of the results obtained on the hydrolysis of PEP. In particular, we will see how occur the formation of the pentacoordinate intermediate **B** and of the cyclic intermediate **C**, which are very similar to intermediates **TBP1** and **2**, respectively, involved in PEP mechanism depicted in Scheme 10.1.
As shown in the proposed mechanism (Scheme 10.4), the 2'-oxygen of the ribose ring firstly attacks the phosphorus atom (Scheme 10.4, structure **A**) acting as an internal nucleophile to generate the cyclic pentacoordinate intermediate or transition state **B**. This attack should be more activated by a factor of ~10^6 fold with respect to any other external nucleophilic attack, such as that with water, which would give formation of a disfavored acyclic pentacoordinate transition state. The cyclic phosphodiester **C** can be obtained by collapse of the pentacoordinate intermediate **B** after departure of the group **O-5'** which is the most apicophilic group in **B**. Now, once formed **C**, which is very similar to compound **2** in PEP mechanism, it can easily undergo an attack, activated by its cyclic form, by the nucleophile H_2O, with formation of the stabilized cyclic pentacoordinate intermediate or transition state **D**, which then collapses, giving the product of hydrolysis **E**.



Scheme 10.4. Proposed mechanism of self-cleavage or hydrolysis of ribozymes with formation of cyclic phosphodiester **C** causing the 3'-5' bond cutting of the RNA chain. Structure **A** represents the 3',5'-phosphodiester linkage in the ground-state configuration. N group represents any of the four natural nucleotide base moieties. Dashed lines depict the continuation of the RNA chain. It is reported[25] that the 5'-thio RNA was cleaved almost two orders of magnitude more rapidly than the parental 5'-oxy RNA substrate. This is in accord with a possible better coordination of Mg ion on sulfur than on oxygen.

It should be noted that the **O-2'** group is more apicophilic and leaving group than **O-3'** in all pentacoordinate cyclic intermediates as those shown in Scheme 10.4. This is due to the presence of the N group (N represent one of the four natural nucleotide base moieties), which is more electron-withdrawing than **C-5'**. In this manner is also explained the exclusive ligation of phosphoryl group in **O-3'** position in the RNA chain. These last steps can also explain the facile elongation of RNA, which is the reverse (normal arrows in Scheme 10.4) of the cleavage reaction (dotted arrows).

It should be noted that on the basis of these different apicophilicities of OH groups caused by the presence of N-base bonded at **C-1'** we can deduce that in the natural formation of a ribonucleotide,

the RNA building block, the attack on the sugar by the N base must occur before the phosphorylation which, consequently, selects the **O-3'** position. In other words, we think that the natural assembling of a ribonucleotide must occur in a "self-organized process" in which probably the first step would be the attack of the nitrogen base on the sugar.

Obviously, in the mechanism depicted in Scheme 9.4, metal ions such as Mg^{++} could play a key role in driving the reaction in one direction or its reverse. For example, coordination of the magnesium ion to the 5' oxygen should favor the apical position of this group and its subsequent departure.
In addition, this mechanism might explain both the difficulty of RNA to undergo hydrolysis and its ability to facilitate chemical transformations such as its elongation process as well as peptide bond formation and transesterification.[27] We suspect that in these transformations the cyclic phosphate **C** is the true "catalyst" of the ribozyme, similar to the cyclic phosphate intermediate **2** of PEP.

10.3 Experimental section

10.3.1 General

NMR spectra were recorded at 300, 400 or 600 MHz for ^{1}H NMR, at 75.45, 100.57 or 150.82 MHz for ^{13}C NMR and at 161.89 MHz for ^{31}P NMR, with Varian Gemini 300, Varian Mercury 400 or Varian Inova 600 instruments. ^{31}P NMR chemical shifts were referenced to external standard 85% H_3PO_4 aqueous solution, ^{1}H and ^{13}C NMR chemical shifts for samples dissolved in pyridine-d5 were referenced to solvent (8.72 and 149.5 ppm for the lowest field signal in ^{1}H and ^{13}C spectrum, respectively); for those dissolved in D_2O, to external 3-(trimethylsilyl)propionic acid; and to CD_3CN (1.93 and 1.26 ppm for ^{1}H and ^{13}C spectrum, respectively).^{13}C and ^{31}P NMR spectra were recorded in a ^{1}H broad-band decoupling mode. *J* values are given in Hz. All commercially available solvents and reagents were >99.5% pure. 2-(Phosphonooxy)acrylic acid (PEP, **1**) was purchased, as potassium or cyclohexylammonium salt, from Sigma-Aldrich.

10.3.2 Structure of 2-(phosphonooxy)acrylic acid (1, PEP) in water

0.015 g (0.073 mmol) of potassium salt of **1** was dissolved in 0.7 mL of D_2O and the solution was poured in a NMR tube. ^{31}P NMR spectrum of the solution showed a signal ascribed to compound **TBP1**, stable in solution for at least four months.

2,2,2-trihydroxy-5-methylene-1,3,2λ^5-dioxaphospholan-4-one (TBP1): ^{31}P NMR (161.89 MHz, D_2O): δ = –3.8 ppm; ^1H NMR (400 MHz, D_2O): δ = 5.74 (dd, *J*= 2.5 Hz, *J*= 2.5 Hz, 1H), 5.40 ppm (dd, *J*= 2.1 Hz, *J*= 2.5 Hz, 1H); ^{13}C NMR (150.82 MHz, D_2O): δ = 166.6 (d, *J*= 6.9 Hz), 144.6 (d, *J*= 7.1 Hz), 109.2 ppm (d, *J*= 3.8 Hz).

10.3.3 Behaviour of compound 1 in acidic aqueous medium

Compound **1** (as potassium salt) was dissolved in 0.7 mL of acidic (DCl) D_2O solution (pD~2). Immediately, the ^{31}P NMR spectrum showed a signal ascribed to compound **TBP1** (δ_{31P} –3.8 ppm) (see above). After about 24 h at room temperature, the ^{31}P NMR spectrum showed presence of a signal at δ +0.5 ppm, corresponding to that of deuterated phosphoric acid (checked through addition of a little amount of an authentic sample of H_3PO_4). After 40 days, ^{31}P NMR spectrum showed the two signals of D_3PO_4/**TBP1** in 40/60 relative height. The reaction was complete after about three months.

The same experiment was carried out at 60 °C in the NMR tube: after one hour the ^{31}P NMR spectrum showed presence of the signal of **TBP1**, a transient signal at δ= +2.4 ppm, probably belonging to compound **2**, the signal of **1-oxo-1-[(tetrahydroxyphosphoranyl)oxy]acetone (4)** (δ_{31P} = –10.0 ppm) and that of deuterated phosphoric acid, in about 100:1:7:15 relative ratio. After 6 hours the only signal detected was that of D_3PO_4.

10.3.4 Behaviour of 2-hydroxy-5-methylene-1,3,2-dioxaphospholan-4-one 2-oxide (2)

Compound **2** was synthesized in pyridine as previously described.[17] Structure of **2** (or of its cyclohexylammonium salt) was ascertained in non-hydrolytic conditions; its spectral data in different solvents are as follows:

^1H NMR (400 MHz, pyridine-d_5): δ = 6.24 (dd, *J*= 2.2 Hz, *J*= 2.2 Hz, 1H), 5.94 ppm (dd, *J*= 1.9 Hz, *J*= 2.2 Hz, 1H); ^1H NMR (300 MHz, CD_3CN): δ = 5.91 (dd, *J*= 2.2 Hz, *J*= 2.2 Hz, 1H), 5.61 ppm (dd,

J= 2.1 Hz, *J*= 2.2 Hz, 1H); ^{13}C NMR (75.45 MHz, CD_3CN): δ = 163.8 (d, *J*= 6.6 Hz, C=O), 144.4 (d, *J*= 7.2 Hz, CC=O), 111.3 ppm (d, *J*= 4.6 Hz, CH_2); ^{31}P NMR (161.89 MHz, $CDCl_3$): δ = +2.1 ppm. Compound **2** (0.010 g) was dissolved in D_2O in a NMR tube: immediately was observed presence, in ^{31}P NMR spectrum, of compounds **TBP1** (δ = –3.8 ppm), D_3PO_4 and **4** in 20:10:1 relative height. At this point, the reaction temperature was raised until 60°C: after two hours a this temperature, only presence of deuterated phosphoric acid was detected.

10.3.5 Addition of methanol at room temperature to pure compound 2

0.010 g (0.074 mmol) of compound **2** was dissolved in anhydrous methanol (0.7 mL) in an NMR tube and kept at room temperature. The ^{31}P NMR spectrum showed a signal corresponding to intermediates **TBP5** and **TBP6** (δ_{31P} = –2.6 ppm). After a few minutes signal of **TBP5** and **TBP6** decreased and concomitantly the signal (δ_{31P} = +2.4 ppm) probably belonging to the methyl cyclic phosphate **5** appeared. After about three hours prevalent presence of **5** was detected. Water was added to this solution and, after one hour ^{1}H NMR and ^{31}P NMR spectra showed presence of methyl dihydrogen phosphate (**6**) (δ_{31P} = +1.5 ppm) and pyruvic acid.

10.3.6 Addition of methanol at 60 °C to PEP (1)

In this case PEP (**1**) was dissolved in dry methanol at 60 °C. We found in the first time a very low signal (δ_{31P} = –3.8 ppm) belonging to intermediates **TBP1** and **TBP2**, then appeared signals of intermediates **TBP5** and **TBP6** (δ_{31P} = –2.6 ppm) and that of the very unstable methyl cyclic phosphate **5** (δ_{31P} = +2.4 ppm). This spectrum showed also two signals at δ_{31P} = –2.3 ppm and δ_{31P} +3.4 ppm corresponding to 2-hydroxy-2,2-dimethoxy-5-methylene-1,3,2λ^5-dioxaphospholan-4-one (derived from a second attack by methanol on intermediate **5**) and to dimethyl pyruvoyl phosphate, respectively. After addition of water we observed immediate formation of methyl phosphate **6** (δ_{31P} = +1.5 ppm) and dimethyl phosphate (δ_{31P} = +2.8 ppm).

10.3.7 Hydrolysis of PEP in the presence of Hg^{++} ions

To a solution of 0.015 g (0.073 mmol) of potassium salt of **1** in water (2.0 mL) 0.022g (0.073 mmol) of $HgSO_4$ was added at room temperature. The reaction course was followed by ^{31}P NMR spectroscopy: the immediate appearance of a signal at δ_{31P} = –4.1 ppm, probably belonging to **Hg-TBP2**, and the concomitant appearance of the signal of phosphoric acid was observed. The reaction appeared complete after about 4 days. When the same reaction was carried out at 60 °C it appeared to be complete after a few minutes.

10.3.8 Hydrolysis of PEP in the presence of Mg^{++} ions

To a solution of 0.015 g (0.073 mmol) of potassium salt of in water (1.0 mL) 0.007g (0.073 mmol) of $MgCl_2$ was added at room temperature. The reaction course was followed by ^{31}P NMR spectroscopy, the appearance after about 20 min. of a signal at δ_{31P} = –4.3 ppm, probably belonging to **Mg-TBP2**, was observed together with the signal of phosphoric acid. The reaction reached the completeness after about 4 months. When this reaction was carried out at 60 °C, its end-point occurred after 4 hours.

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7. In a turnstyle rotation (TR), permutation is postulated to occur by mutual counterrotation of a pair (one apical and one equatorial ligand) and of a trio (one apical and two equatorial ligands) with subsequent collapse to a new trigonal bipyramid. In four- and five-membered cyclic phosphoranes the ring must always play the role of the pair. The consequences of single and multiple TR processes follow from the application of the following rules. For TR, transpose the pair ligands and rotate the trio of ligands 120° in the direction that brings the trioapical ligand into the original position of the trioequatorial ligand which remains equatorial in the isomerization. For $(TR)^2$, do not change the pair; rotate the trio as for TR. For $(TR)^3$, transpose the pair. For a discussion of the permutational isomerization of phosphoranes by the TR process, see ref. 7b.
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Chapter 11

FIRST PREBIOTIC GENERATION OF A RIBONUCLEOTIDE FROM ADENINE, D–RIBOSE AND TRIMETAPHOSPHATE[1]

11.1 Intoduction

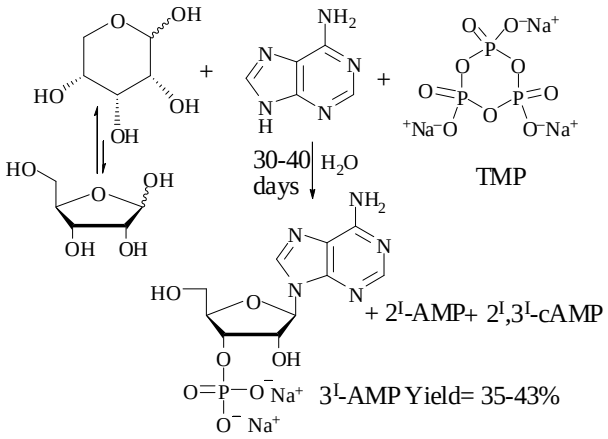
The idea that RNA might have formed spontaneously at some stage on early Earth has inspired many searches for obtaining some feasible prebiotic syntheses of ribonucleotides, the building blocks of RNA.[2] For many years, efforts to understand the prebiotic synthesis of a ribonucleotide have been based on the assumption that a ribonucleotide could have assembled from three molecular components: a nucleobase, a ribose sugar and a phosphate. But, so far, the main difficulties have been in how to combine these three components.[3,4] In particular, the most frustrating has been the failure to find an efficient procedure[4b,5] to join together the nucleobase and the ribose thus casting doubt on the feasibility of these molecules to spontaneously combine in the primordial Earth. For this reason, the idea that a molecule as complex as RNA could have assembled spontaneously from its components now is viewed with increasing scepticism.[3] Recently, Sutherland *et a*l.[6] accepting the impossibility of a spontaneous assembling of the three simple components have explored a totally different approach for pyrimidine ribonucleotide synthesis in which the sugar and the nucleobase emerge from a common precursor after several steps in different reaction conditions.

11.2 Results and discussion

Now, we report[1] that a spontaneous self-assembling of the three components is permitted giving natural adenosine monophosphates (AMP) as final products. In fact, a very feasible synthesis of a ribonucleotide (adenosine monophosphates), from its three molecular components, a nucleobase (adenine), a sugar (D-ribose) and a phosphate (trimetaphosphate or P_4O_{10}), occurs giving adenosine monophosphates in good yields. The synthesis is made in aqueous solution and in a have postulated,[7] on the basis of experimental data, that the evolution of life should be governed or driven by a

mechanism in which the formation of cyclic pentacoordinate phosphorus intermediates is more activated of 10^{6-8} fold with respect to other collateral processes.[8]

In other words, it is necessary to find primordial phosphorylating reagents containing the phosphate group belonging to a cycle in order to obtain very activated cyclic pentacoordinate phosphorus intermediates.[9] One of the primordial cyclic reagents was very likely P_4O_{10}. The discovery of Yamagata[10] demonstrating that P_4O_{10} and its derivatives as trimetaphosphate (TMP) are produced from volcano magma is, in this context, very important. TMP is a very stable cyclic compound containing three phosphate groups used for condensation and phosphorylation reactions.[11] For this reason we began to study the possibility to obtain a ribonucleotide (adenosine phosphates) by a simple reaction in aqueous solution of a mixture of D-ribose, adenine and a cyclic phosphate as TMP (Scheme 11.1), monitoring for 60 days two types of reactions: one with a highly concentrated mixture of the three components in water, and another at high dilution.



Scheme 1. One-pot generation of adenosine monophosphates in aqueous solution from adenine, D-ribose and sodium trimetaphosphate

It should be noted that D-ribose in solution is in equilibrium between different forms (α-pyranose 20%, β-pyranose 60%, α-furanose 5%, β-furanose 15%).[12] Then, the formation of natural adenosine, adenine b-ribofuranoside, can be obtained together with other isomeric forms derived from the reaction between adenine and other isomers of ribose. It should be noted that the four forms of adenine ribofuranosides and adenine ribopyranosides are in equilibrium.[13] Then, in our process it will be necessary to consider these equilibria, the different possible nucleosides,[3b,c] and to understand if, at the end of the reaction, a preferential formation of some isomers could occur. As first attempt we performed a reaction at high concentration (~0.1 M) of the reagents and at a pH value in the range 7.0–6.5. Trisodium salt of TMP (459 mg, 1.5 mmol), D-ribose (150 mg, 1.0 mmol) and adenine (135 mg, 1.0 mmol) were added in 10 mL of water (a small amount of sodium azide was added as an aseptic) in a 1.5 : 1 : 1 relative molar ratio (pH ≈ 7.0). At this concentration value adenine, being

much less soluble with respect to the two other reagents, remains partially undissolved. The initial pH (pH ≈ 7.0) was that obtained after introduction of the three components in water. Variations of pH until the final value of 6.5 are due to the very slow hydrolysis of trimetaphosphate with formation of phosphoric acid which forms a salt with the remaining adenine. In these conditions, the final yield of adenosine monophosphates is very low, about 10%. Subsequently, we have carried out a reaction at high dilution in which all the reagents were completely dissolved and probably some eventual collateral reactions are minimized. The reaction was carried out in water solution (pH ≈ 7.0–6.5) with high dilution of the three reagents (1.85×10^{-4} M). Adenine (50 mg, 0.37 mmol), D-ribose (55 mg, 0.37 mmol), and trisodium salt of TMP (168 mg, 0.55 mmol) were dissolved in 2 L of aseptic water, in a 1 : 1 : 1.5 relative molar ratio. The reaction course was followed by HPLC and, after lyophilization, by ^{1}H and ^{31}P NMR spectroscopy. Very probably, the first step that occurs in the mixture is the attack of TMP on the anomeric OH group of ribose isomers giving unstable pentacoordinated intermediates (see intermediates **A**, **B**, and **C** in the mechanism). In the second step we have condensation of adenine with concomitant formation of AMPs and adenosine isomers. In fact, in the first time of the reaction (5 days) we observed by HPLC the formation of AMPs and adenosine isomers in a ratio of about 1 : 1. The adenosine isomers are adenosine β-ribofuranoside and adenosine α-ribofuranoside (in a relative ratio of about 6 : 1 calculated from ^{1}H NMR of a reaction mixture). They have been assigned on the basis of a comparison with the isomers obtained by keeping natural adenosine for several days in aqueous solution. In these conditions a slow isomerization of adenosine occurs and the two isomers, adenosine β-ribofuranoside and adenosine α-ribofuranoside, have been identified by comparison of their ^{1}H NMR data with the published[13] chemical shifts for the adenosine isomers. After about 25 days we have as major product AMPs in which the 3'-AMP and 20'AMP are in a ratio of about 3 : 2. A small amount of cyclic 2',3'-AMP (2',3'-cAMP) was also observed.

After about 45 days we have a total disappearance of 2',3'-cAMP and a gradual decrease of the relative amount of the different adenosine monophosphates indicating a probable formation of short oligonucleotides that might arise from the cyclic phosphate and 5'-OH of 3'-AMP. The AMPs are separated by preparative HPLC. The structures have been assigned by ^{1}H NMR by comparison with authentic commercial samples. The total yield, after about 30–40 days, in adenosine monophosphates, is of about 35%. No traces of ATP or 5'-AMP were detected by HPLC and ^{31}P NMR spectroscopy. Then, the global process is highly regio-, chemio-, and stereoselective because we found only AMP in β-furanose forms which are the natural nucleotides. It should be noted that in the literature[14] is reported a similar phosphorylation reaction with commercial samples of adenosine and TMP (or P_4O_{10})[10b] in different reaction conditions. The reported[14a,b] results are very close to our data with

exclusive formation of 2'- and 3'-adenosine phosphates and exclusion of 5'-AMP and ATP. The reported[4b] very low yields (4%) of natural adenosine obtained by adenine and D-ribose with TMP at 100 °C for several hours could be explained by the concomitant formation of adenosine phosphates (or by the decomposition and isomerization[13] of adenosine at 100 °C) which were not considered by the authors. Our relatively low yield (35%) might be due to the lack of free adenine in the solution due to the formation, after about 30 days, of a small amount of phosphoric acid which forms a salt with the remaining adenine. In the light of these considerations, and in order to increase the yields of reaction products, we carried out the reaction with an excess of adenine. In particular, when we used adenine, D-ribose, and TMP in 1.2 : 1 : 1.5 relative molar ratio and in these conditions, after 35–40 days, the yields in adenosine monophosphates reached 43% with respect to the ribose. When the reaction is carried out with equimolar amounts of the three reagents we obtained after about 30 days formation of relevant amount of AMP isomers indicating that TMP is reformed after the first step or gives directly the AMPs without relevant formation of adenosine (see Scheme 11.2).

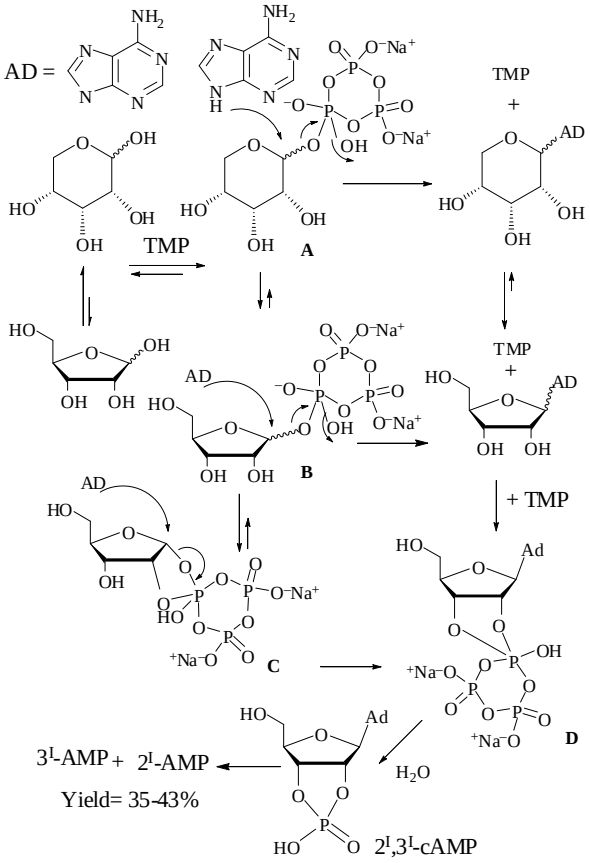
Preliminary results show that a similar reaction occurs with guanidine obtaining guanosine phosphates.

Finally, it has to be noted that the use of P_4O_{10} instead of TMP gave a similar behaviour but with minor yields in AMP because of its major instability in water that gives rise, after several days, to phosphoric acid which forms a salt with adenine.

It should be noted that the process is activated when in the solution Mg^{2+} ions are present.[4,11] Actually, in this case the reactions reached the end after only 20 days (yield in adenosine monophosphates is of about 45%) thus suggesting that the magnesium ions act as catalysts for all the process (both condensation and phosphorylation). Very likely, the first step of this reaction is the preferential phosphorylation (by TMP) of the hydroxy anomeric group of the ribose, which is the most reactive, to give ribose-1-TMP as pentacoordinated phosphorus intermediates **A** and **B** (Scheme 11.2). The TMP group is a very good leaving group and could activate a second step, involving the subsequent nucleophilic attack of adenine from the opposite side with reformation of TMP thus producing adenosines (probably[15] in furanose forms). However, it is also possible that a bicyclic pentacoordinate phosphorus intermediate **C** is preferred[9] over **A** and **B** for its two cycles around the P atom. In this case, the attack of adenine is now obliged to go in the opposite side of the O-group giving the new intermediate **D** which can be formed also by direct attack of TMP on β-adenosyl furanoside.

The hydrolysis of intermediate **D** gives 2',3'-cAMP which by subsequent hydrolysis gives 2'-AMP and 3'-AMP. The attack of TMP on adenosines to give phosphorylated adenosines is probably driven both by the position of the adenylic moiety and by the presence of the two OH groups in the *cis*

relative position of the ribose moiety in the adenosine ribofuranoside form. In the adenosine ribopyranoside form the position of the two OH groups is disfavored to form a cyclic phosphate. It is reported[15] that the transformation of ribose into its cyclophosphates belongs to the functionalizations of the ribose molecule which selects the furanose form from the sugar's furanose/pyranose equilibrium. For this reason we found only adenosine β-ribofuranoside monophosphates, determined by their ^{1}H NMR. These factors conduct to the preferential formation of 2',3'-cAMP that in aqueous solution can be hydrolyzed to adenosine-2'-phosphate and adenosine-3'- phosphate (Scheme 11.2). In this manner the 5'-hydroxy group remains free, thus explaining why we could detect neither 5'-AMP nor ATP. It is reported[14a] that when deoxyadenosine is reacted with TMP, only 3'- and 5'-monophosphates are obtained in very low yield (2%) suggesting a disfavored formation of a 3',5'-cyclic phosphate. This is in good accord with our mechanism which is also in agreement with reported data in which it has been observed[4b] that when α- and β-D-ribofuranose-1-phosphate or any phosphate-containing products were heated with adenine no formation of adenosines was observed. This is in accord with the formation of unstable intermediates such as **A**, **B**, and **C**. It is reported[16] that in some cases the 9-N in adenine is the prevalent position of a nucleophilicattack.



Scheme 11.2. Proposed reaction mechanism.

11.3 References

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Chapter 12

FACILE SYNTHESIS OF HYDANTOINS AND THIOHYDANTOINS IN AQUEOUS SOLUTION[1]

12.1 Introduction

After the discovery of the spontaneous, and prebiotic, formaton of ribonucleotides (Chapter 10), we have focalized our actention to the synthesis of the costituents of RNA (sugar, nitrogen bases). In particular we want studied the synthesis of the nucleobases in prebiotic condiction.
For our synthesis we have choise the uracile as target molecule (figure 12.1).

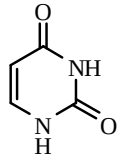


Figure 12.1. Structure of uracile.

As starting material we have hypothesized a urea, and glyceraldehyde, that certly two prebiotic compounds, and as condensantig agent, we use in first time trimetaphosphate but the reaction don't occur, after we have traied with phosphoric anidhride, P_4O_{10}, also this compound was present in the primordial Earth.
The reaction with P_4O_{10}, don't give uarcile, as we expected. The study of the reaction mixture have shown the presence of 5-methylhydantoin, that are five member heterocyclic compounds (figure 12.2).

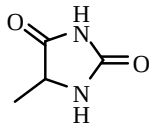
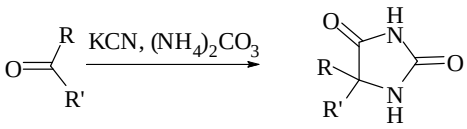


Figure 12.2 5-methylhydantoins.

Hydantoins and thiohydantoins are compounds that have a reactive urea (or thiourea) core. They are an important structural moiety found in several natural products and pharmacologically important compounds.[2-6] They are well known for diverse biological activities and play a key role as antiarrhythmics,[7] anticonvulsants,[8] antitumor compounds,[9] aldose reductase inhibitors,[10] anti-inflammatory compounds,[11] and antiandrogens.[12]

Synthetically, hydantoins are important precursors of amino acids, via either acid-, base- or enzyme-catalysed hydrolysis. The Bucherer–Bergs reaction[13] (Scheme 12.1) is the most commonly used method for the synthesis of hydantoins. This multicomponent reaction starts from an aldehyde or a ketone whose ready availability makes the Bucherer–Bergs reaction an attractive method for the synthesis of hydantoins. However, the use of KCN lead to problems on safety, causing the reaction to often be conducted within a sealed tube at a temperature of 80 °C. One improvement on the Bucherer-Bergs reaction has been the use of ultrasonication.[14]



Scheme 12.1. Bucherer–Bergs reaction.

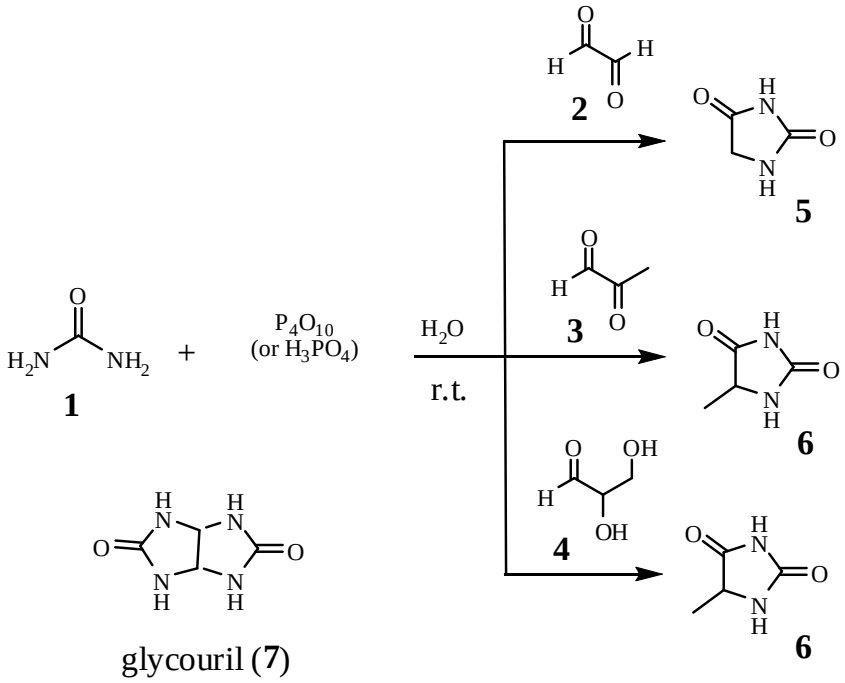
Other methods furnishing hydantoins include the treatment of amino amides with triphosgene,[15] the reaction of amino acids with acetic anhydride and ammonium thiocyanate (to give the thiohydantoins),[16] the combination of carbodiimides with unsaturated carboxylic acids, and the treatment of nitriles with organometallic reagents followed by addition of potassium cyanide and ammonium carbonate.[17,18] Both microwave[19] and solid phase[20,21] technologies have been employed in the synthesis of hydantoins. There are also more esoteric syntheses of hydantoins that involve complex rearrangements.[22,23] Several syntheses of thiohydantoins have also been reported.[16,24]

Now we wish to propose a three components synthesis of some simple hydantoins and thiohydantoins using as starting materials compounds available in the primordial Earth.

These compounds are urea, glyoxal (and its simple derivatives) and P_4O_{10}, very likely one of the first primordial condensing reagents. The discovery of Yamagata[25] demonstrating that P_4O_{10} is produced from volcano magma is, in this context, very important. In other words, P_4O_{10} is certainly a prebiotic reagent which can be involved in several reactions[25b] as phosphorylation, condensation, dehydration, dealcoholysis, and many others.

12.2 Results and Discussion

The synthesis of hydantoins is made in aqueous solution in a 'one-pot' manner or by adding separately the three reagents (urea or N-methylurea, glyoxal, and P_4O_{10}) at room temperature.
The results are summarized in Schemes 12.2 and 12.3.

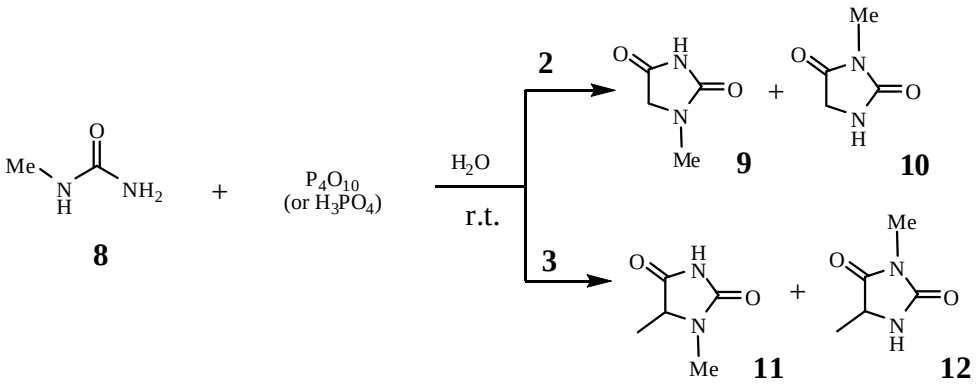


Scheme 12.2. Hydantoins from urea (**1**) and aldehydes **2**–**4**.

The best yields (60–70%) are obtained when the reagents are added separately with first addition of aldehyde (1 mmol) to P_4O_{10} (1 mmol) and then urea (1 mmol). Similar yields (50–60%) are obtained when the reagents are dissolved simultaneously in water (one-pot manner).
The hydantoins are separated from the reaction mixture after partial removal of water by lyophilization "in vacuo" followed by continuous liquid/liquid extraction of the aqueous residue with ethyl acetate. The yields are of about 60–70%, depending on the number of extractions.

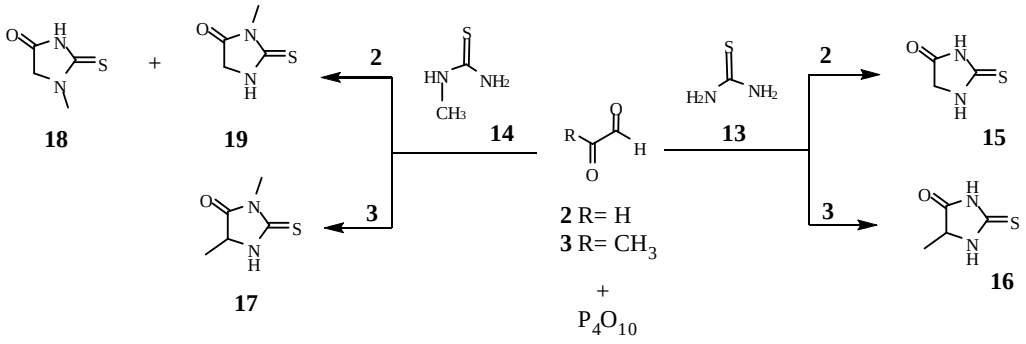
When we used two eq of urea and one eq of glyoxal and P_4O_{10} we obtained as maior product glycouril (**7**), in 75% yield, that crystallized from the aqueous solution.[26] This class of compounds is also of interest for its biological activity, in particular psychotropic activity.[27]

When we used N-methylurea (**8**) we obtained a mixture of the two isomers **9** and **10** (or **11** and **12**) in a relative molar ratio of 70:30 (Scheme 12.3).



Scheme 12.3. Hydantoins from N-methylurea (**8**) and aldehydes **2** and **3**.

In similar manner we have obtained several thiohydantoins **15**–**19** (See Scheme 12.4). It should be noted that in the reaction between aldehyde **3** and N-methylthiourea **14**, we obtain only one of the two possible isomers, in particular, we established, by ^{1}H NOE NMR experiment, that the structure of the product is that of compound **17** (see Scheme 12.4).



Scheme 12.4. Thiohydantoins from thiourea (**13**) or N-methylthiourea (**14**) and aldehydes **2** and **3**

All products have been identified by ^{1}H NMR and GC-MS spectroscopy and their spectral data have been compared with those reported in literature.

The method is attractive for its simplicity since it requires only the blending of the three components in aqueous solution and at room temperature for ten minutes.

It should be noted that the synthesis can be carried out also with a large excess of 85% aq. H_3PO_4 (2.5 mmol), but in this case the reaction time is of two hours and the yields are lower (50–60%). It is also known[28] that the same hydantoins can be obtained using HCl but in this case the reaction was carried out at 90 °C for one hour. The reaction carried out with NaOH at room temperature do not give hydantoins.

12.3 Reaction mechanism

It is known that cyclic phosphorus compounds containing a phosphoryl group react with a nucleophile faster (of a factor of 10^{6-8}) with respect to the corresponding acyclic compound, to give the relative pentacoordinate species.[28a] This is due to the major stability of this cyclic pentacoordinated intermediate than the corresponding acyclic pentacoordinated intermediate.

P_4O_{10} has a polycyclic structure while H_3PO_4 has an acyclic structure (Figure 12.3): based on the above considerations, we can predict that P_4O_{10} would react faster than H_3PO_4, as the experimental data have confirmed.

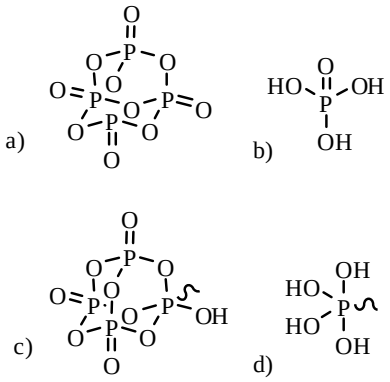
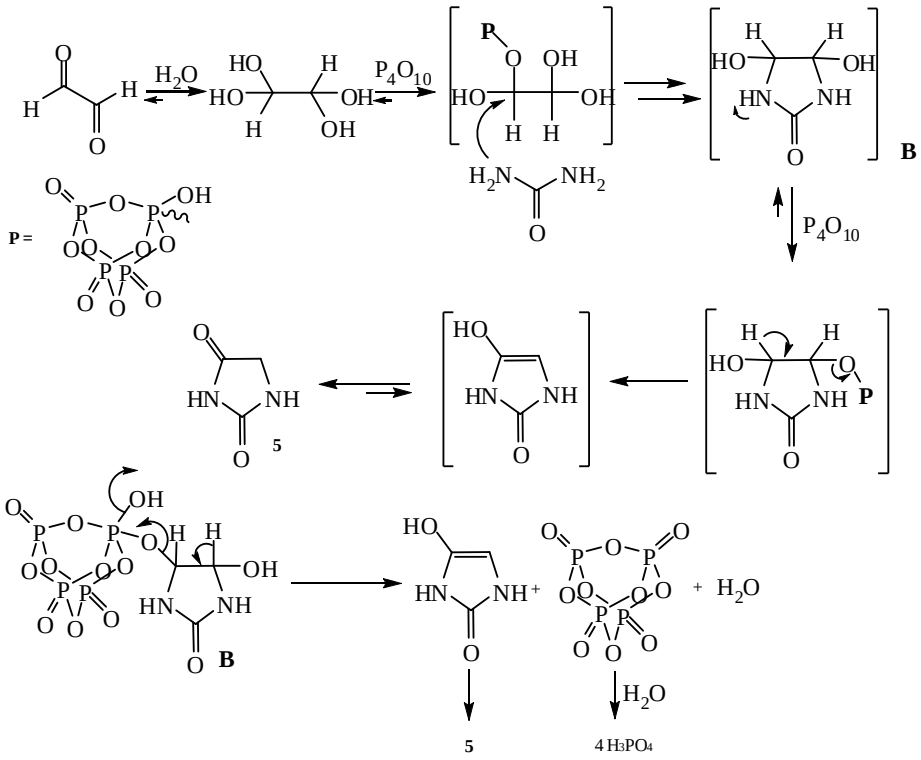


Figure 12.3. Structures of: P_4O_{10} (a), H_3PO_4 (b), and their relative pentacoordinate species (c) and (d).

From these data we proposed the reaction mechanism reported in Scheme 12.5.



Scheme 12.5. Proposed mechanism of formation of hydantoin **5** from glyoxal.

The initial step probably involves the hydration of the aldehyde and then the phosphorylation by P_4O_{10} of two hydroxy-groups with formation of the intermediate **A** which is stable. It is important to emphasize that in the case of P_4O_{10} this step is very fast, while when H_3PO_4 is used, this kind of intermediate is disfavored because the corresponding intermediate A-like is not a cyclic pentacoordinated intermediate, as in the case of P_4O_{10}, which is stabilized[28] by a factor of 10^{6-8} with respect to the corresponding acyclic intermediate. The subsequent nucleophilic attack of urea gives condensation and cyclization with probable formation of intermediate **B** which collapses to hydantoin. In the process there is reformation of P_4O_{10} as shown in the decomposition of intermediate **B**. This is supported by the fact that in the ^{31}P NMR spectrum of the reaction mixture we noted always the signal of P_4O_{10} (δ = -23 ppm), also at the end of the reaction. Only after some days we noted the signal of H_3PO_4 due to the partial hydrolysis of P_4O_{10}. In addition, the reaction goes to the end with the same product yield even when it is carried out with only 0.5 eq of P_4O_{10}. In the case of other aldehydes, a mechanism analogous to that depicted in Scheme 5 could occurr.

12.4 Experimental section

12.4.1 General

^{1}H and ^{31}P NMR spectra were recorded at 300 and 121.45 MHz, respectively. Chemical shifts are referenced to the solvent (δ = 2.50 ppm for ^{1}H NMR in DMSO–d_6 and to external standard aq. 85% H_3PO_4 for ^{31}P NMR). J values are given in Hz. GC-MS analyses were performed on an gas chromatograph equipped with a (5%-phenyl)-methylpolysiloxane column (30 m length, 0.250 mm. i.d., 0.25µm thickness), interfaced to a quadrupole mass detector. Mass spectra were recorded at an ionisation voltage of 70 eV in the EI mode.

12.4.2 Synthesis of hydantoins and thiohydantoins. General procedure

To a stirred solution of aldehyde (0.6 mmol) in H_2O (10 mL), P_4O_{10} (170 mg, 0.6 mmol) was added. After 5 minutes urea (or thiourea) (0.6 mmol) was added, and the mixture was stirred at room temperature for 10 minutes. The solvent was partially removed by lyophilization “in vacuo” and the product was isolated from the crude residue through several liquid/liquid extractions with ethyl acetate. After removal of the organic solvent, the product was purified by flash chromatography or by simple crystallization. The yields were in the range 60–70% and are depending on the number of extractions.

12.4.3 Synthesis of hydantoins using H_3PO_4

To a stirred solution of aldehyde (0.6 mmol) in H_2O (10 mL), aq. 85% H_3PO_4 (170 µL, 2.5 mmol) was added. After 5 minutes urea (0.6 mmol) was added, and the mixture was stirred at room temperature for 10 minutes. The GC–MS analyses shows the presence of the product but in very low amount. The end of the reaction occurred after two hours and the corresponding hydantoins were obtained in 50-60% yield.

Imidazoline-2,4-dione (**5**) (Hydantoin): white solid; yield: 63%; m.p. 222–223 °C (Lit.:[30] 221–223 °C), ^{1}H NMR (300 MHz, DMSO-d_6) δ= 10.58 (bs, 1 H), 7.65 (bs, 1 H), 3.85 (s, 2 H); MS (m/z, %): 100 (M^+, 100), 72 (45), 57 (20).

5-Methylimidazoline-2,4-dione (**6**) (5-methyl hydantoin): white solid; yield 60%; m.p. 146–148 °C (Lit.:[31] 147–148 °C) ^{1}H NMR (300 MHz, DMSO-d_6) δ= 10.60 (bs, 1 H), 8.00 (s, 1 H), 4.03 (dq, J_1-Me= 7.1 Hz, 1 H) 1.25 (d, J_1-5= 7.1 Hz, 3 H); MS (m/z, %): 114 (M^+, 100), 99 (22), 86 (73), 71 (28).

Tetrahydroimidazo[4,5-d]imidazole-2,5(1H,3H)-dione (**7**) (glycouril): white crystal; yield 68%; m.p. 357 °C (dec.) (Lit.:[27] 360 °C, dec.), ^{1}H NMR (300 MHz, DMSO-d_6) δ= 7.14 (s, 4 H), 5.23 (s, 2 H); ES^+: (m/z) = 143 (M + H), 165 (M + Na).

1-Methylimidazoline-2,4-dione (**9**): (1-methyl hydantoin) white solid; yield 35%; m.p. 156–158 °C (Lit.:[32] 158 °C), ^{1}H NMR (300 MHz, DMSO-d_6) δ= 10.70 (bs, 1 H), 3.91 (s, 2 H), 2.80 (s, 3 H); MS (m/z, %): 114 (M^+, 100), 96 (5), 86 (17), 73 (17); 58 (51).

3-Methylimidazoline-2,4-dione(**10**): (3-methyl hydantoin) white solid; yield 30%; m.p. 183-184 °C (Lit.:[33] 185–186 °C), ^{1}H NMR (300 MHz, DMSO-d_6) δ= 7.63 (s, 1 H), 3.85 (s , 2 H), 3.00 (s, 3 H); MS (m/z, %): 114 (M^+, 100), 96 (6), 86 (6), 70 (8); 56 (4).

1,5-Dimethylimidazoline-2,4-dione (**11**): (1,5-dimethyl hydantoin) white solid; yield 33%; m.p. 132–133 °C (Lit.:[34] 131 °C), ^{1}H NMR (300 MHz, DMSO-d_6) δ= 10.73 (bs, 1 H) 3.97 (q, J = 7.0 Hz, 1 H), 2.80 (s, 3 H), 1.28 (d, J= 7.0, 3 H); MS (m/z, %): 128 (M^+, 100), 113 (97), 100 (2), 83 (1); 70 (29), 56 (41).

3,5-Dimethylimidazoline-2,4-dione (**12**): (3,5-dimethyl hydantoin) white solid; yield 37%; m.p. 111–113 °C (Lit.:[35] 110–111 °C), ^{1}H NMR (300 MHz, DMSO–d_6) δ= 7.68 (bs, 1 H), 4.08 (dq, $J_{1\text{-Me}}$= 7.1 Hz, $J_{1\text{-}5}$= 1.3 Hz, 1 H) 3.05 (s, 3 H), 1.50 (d. J= 7.1 Hz, 3 H); MS (m/z, %): 128 (M^+, 100), 113 (14), 100 (38), 85 (5); 70 (11); 58 (46).

2-sulfanylideneimidazolidin-4-one (**15**): (thiohydantoin) yellow solid; yield 61%; m.p.= 228–230 °C (Lit.:[36] 229–231 °C); ^{1}H NMR (300 MHz DMSO–d_6) δ= 11.64 (s, 1 H), 9.91 (s, 1 H), 4.12 (s, 2 H).

5-methyl-2-sulfanylideneimidazolidin-4-one (**16**): (5-methyl thiohydantoin) pale yellow solid; yield 70%; m.p.= 163–166 °C (Lit.:[36] 165–166 °C); ^{1}H NMR (300 MHz DMSO–d_6) δ= 11.59 (s, 1H), 9.98 (s, 1H), (dq, J_1= 7.0 Hz, J_2= 1.5 Hz, 1H), 1.26 (d, J_1= 7.0 Hz, 3H).

3,5-dimethyl-2-sulfanylideneimidazolidin-4-one (**17**): (3,5-dimethyl thiohydantoin) yellow solid; yield 66%; m.p.= 171–172 °C (Lit.:[37] 170–173 °C); ^{1}H NMR (300 MHz DMSO–d_6) δ= 10.29 (bs, 1H), 4.26 (dq, J_1= 7.0 Hz, J_2= 1.0 Hz, 1H), 3.04 (s, 3H), 1.27 (d, J_1= 7.0 Hz, 3H).

1-methyl-2-sulfanylideneimidazolidin-4-one (**18**): (1-methyl thiohydantoin) pale yellow solid; yield 15%; m.p.= 223-224 °C (Lit.:[38] 222-224 °C); ^{1}H NMR (300 MHz DMSO–d_6) δ= 11.59 (s, 1H), 4.15 (s, 2H), 3.08 (s, 3H).

3-methyl-2-sulfanylideneimidazolidin-4-one (**19**): (3-methyl thiohydantoin) yellow solid; yield 53%; m.p. = 166-168 °C (Lit.:[24a] 167–168 °C); ^{1}H NMR (300 MHz DMSO–d_6) δ= 10.12 (s, 1H), 4.10 (s, 2H), 3.05 (s, 3H).

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CONCLUSIONS

In conclusion we think that the origin of life is due fundamentally to the volcanoes activity that have brought to the surface of the earth heat, water, and a great mixture of organic compounds which are essential for the origin of life.

However the big question is: what happened next?

We tried to respond to this question. On the basis of our precedent studies on abiotic chemistry of phosphorus, we have hypotesized that phosphorus containing compounds (in particular cyclic species) may have played a key role in the origin of life.

In fact we found that simple phosphorus cyclic compounds, as P_4O_{10} or $P_3O_{9,}$ present in the volcano magma, 6could be very important in the primordial Earth, activating a reaction by a factor $10^{6\text{-}8}$, minimizing other collateral reactions through the formation of very activated hypercoordinated species that drived only some processes favouring the start of the life.

These processes occur in a prebiotic soup where the most proper place had to be a lake near to an active volcano which, as a chemist, provides the reagents to carry out some important reactions for the evolution of life.

Chapter 13

SYNTHESIS AND MOLECULAR STRUCTURE FOR COMPLEXES FORMED BY LITHIUM COMPOUND AND AMINOMETHYLPHOSPHONIC ACID

13.1 Introduction

Since the isolation of 2-aminoethylphosphonate,[1] natural compounds containing phosphorus-carbon bond[2,3] have been subject to many research. In particular amino-phosphonic (or -phosphinic) acids are study in many field of chemistry, for their biological applications,[4] and also for the industrial interest[5], because some of them are commercial products as herbicides.[6,7]

The aminophosphonic acids are the equivalent phosphorylate of the amino acids. In literature are reported some method for the synthesis of this class of compounds.[8-11]

Recently, studies concerning metal complexes of phosphonic amino acids are receiving considerable interest, because some of these complexes are potential anticancer.

The structures of the amino phosphonic acid metal-complex vary from discrete molecules to polymers.[12-18]

In literature was reported some structural analysis for the complexes between aminomethylphosphonic acid (AMP) (aminophosphonic acid equivalent of glycine) and metal atoms[19-23] and for the free acid.[24]

Herein we report, for the first time, the synthesis and structural characterization for the lithium complexes of aminomethylphosphonic acid (AMP). Moreover we investigated the influence of the reaction conditions and the crystallization methods on the structure outcome.

13.2 Results and discussion

We wished to examine the outcome of the reaction between aminomethylphosphonic acid (AMP) with lithium compounds, changing the reaction conditions, kind of lithium compound and method of crystallization.

In particular, we studied four reactions which led to obtain three different crystalline structures.

All structures are characterized by similar asymmetric units, where a molecule of AMP is bonded with lithium atom, which is coordinated with a molecule of water. In one case we obtain a dimmer of this structure (see Figure 13.1).

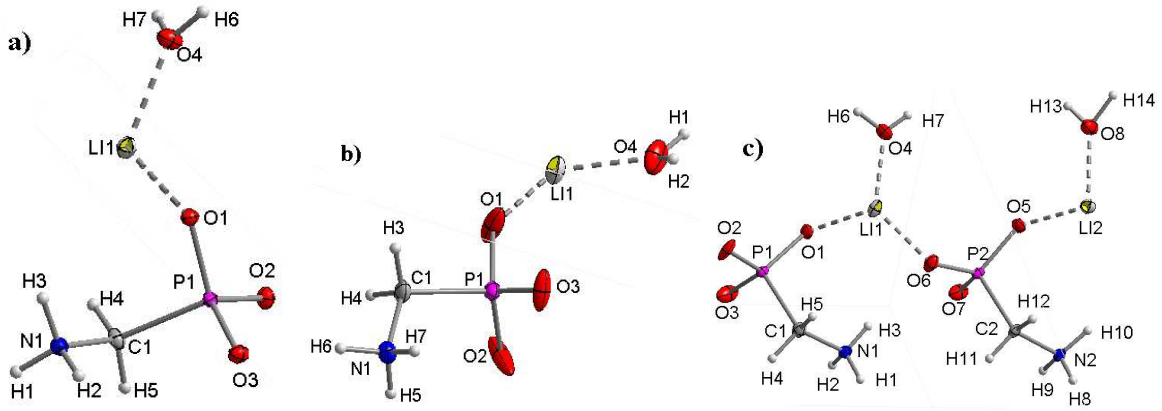

Figure 13.1. Asymmetric unit: a) Asymmetric unit of reaction between AMP+LiOH 1/1; b) Asymmetric unit of reaction between AMP+LiOH 1/1 with methanol as co-solvent for the crystallization; c) Asymmetric unit of reaction between AMP+Li_2CO_3 1/1.

First reaction was carried out mixing AMP and LiOH in water in stoichiometric amount. The crystallization occurred at room temperature by evaporation of the solvent.

We obtained a suitable single crystal. X ray diffractometry analysis showed that the structure is characterized by plans whose lattice is formed by eight-member rings and sixteen-member rings (see figure 13.2).

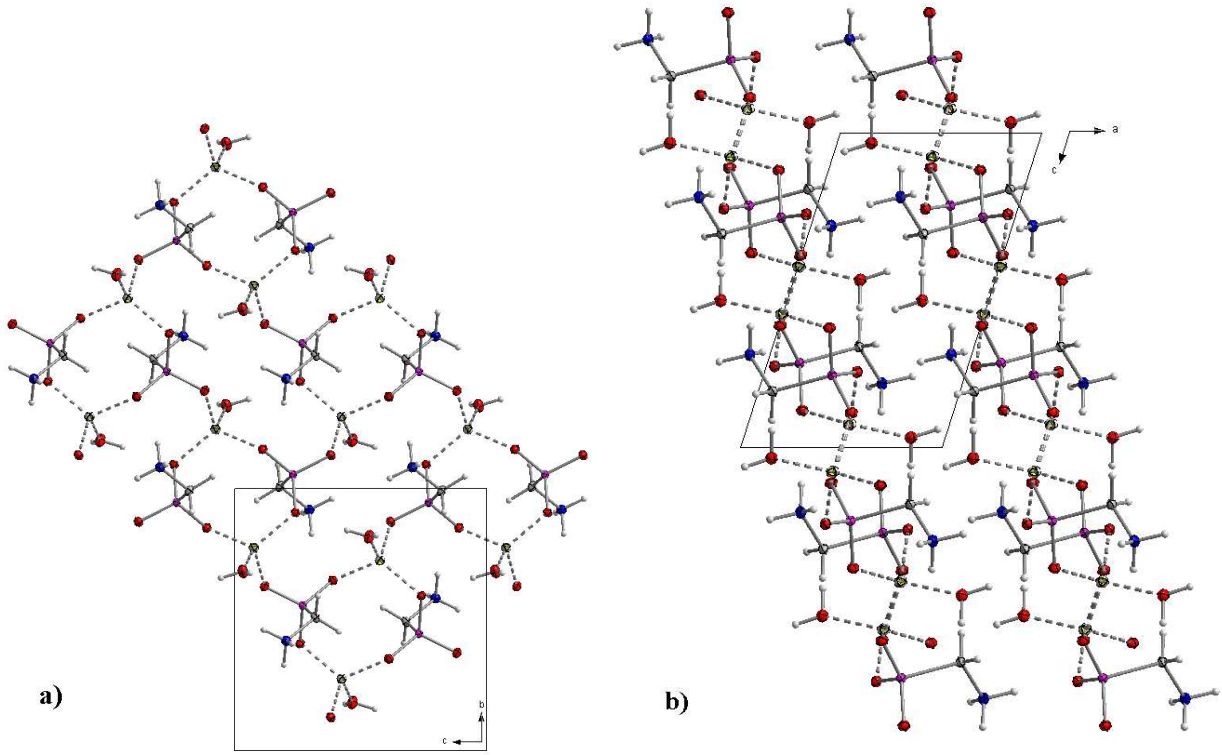

Figure 13.2 Structure of AMP+LiOH. a) View of plan locking along the a axis, where it is clear the presence of the eight-member rings and the sixteen-member rings; b) view of plans locking along the b axis, where it is note the reciprocal disposition of the plans.

Second reaction was carried out with a double amount of LiOH, and the other reaction conditions were the same as the first reaction. X ray diffractometry analysis showed that the structure is the same to that of the first reaction.

In this structure is present an inversion center localized in the center of the unit cell (see figure 13.3).

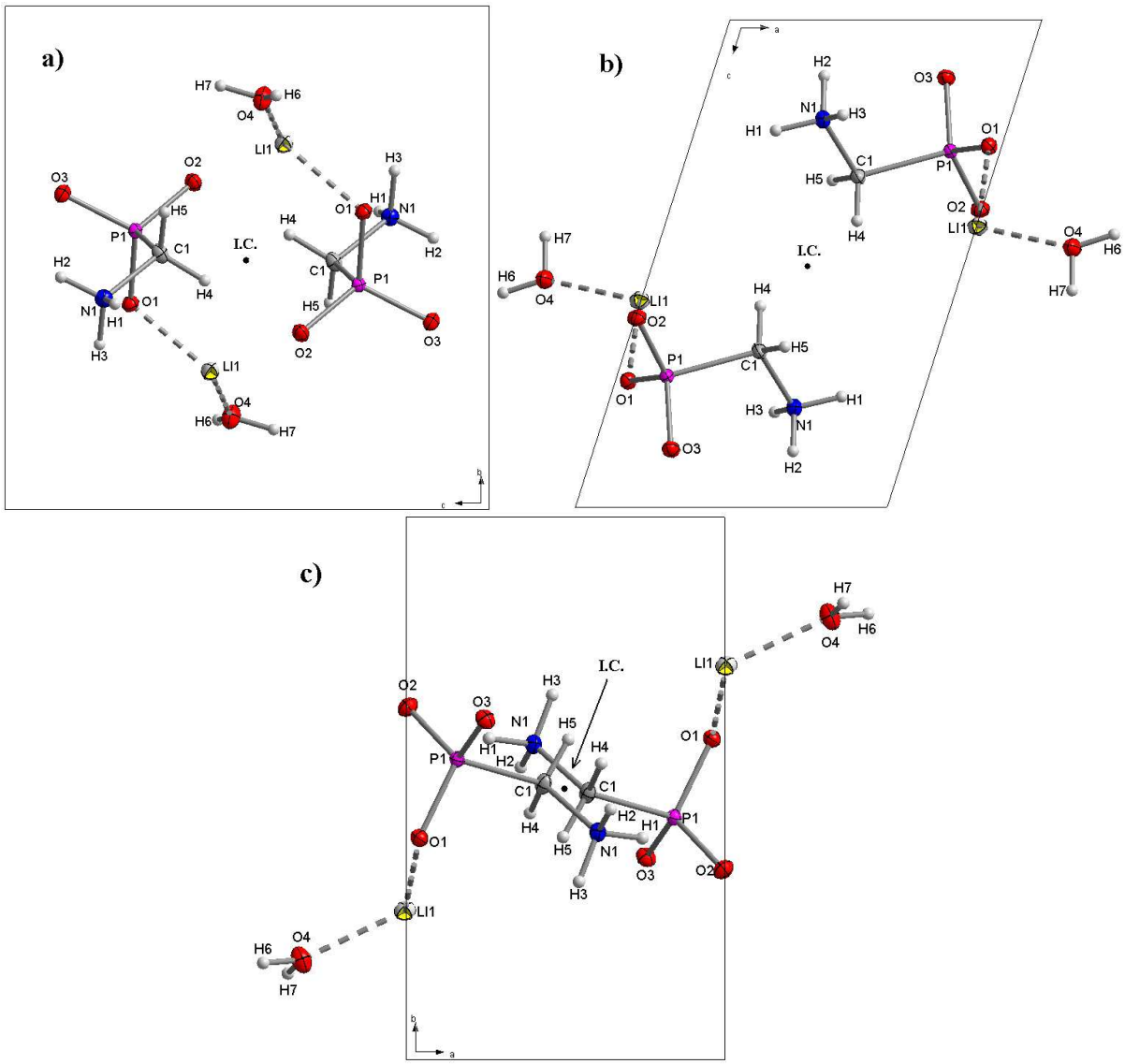

Figure 13.3 Inversion center. Position of the inversion center.

In the third reaction we changed the crystallization methodology, using methanol as co-solvent, the other reaction condition remained the same of the other reactions. In this case we obtained the asymmetric unit similar to the other two previously described, but the lattice structure is characterized by chains formed by eight-member rings alternating with four-member rings (see figure 13.4).

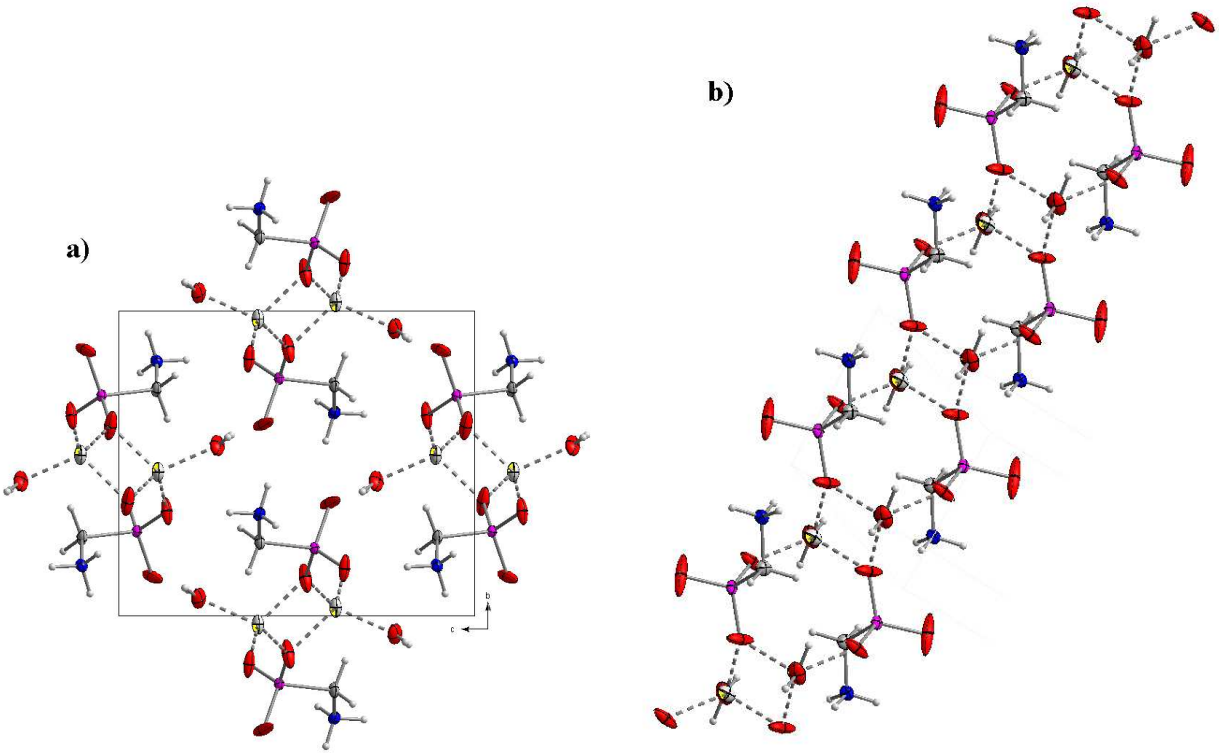

Figure 13.4 Structure of AMP+LiOH crystallized with methanol. a) Unit cell locking along the a axis, b) chain, where is clear the presence of eight-member rings and the four-member rings.

The last reaction was performed with a different lithium compound. We used Li_2CO_3 in stoichiometric amount.

Also in this case we obtained a structure characterized by chains as that of the third reaction, but the asymmetric unit is a dimer (see figure 13.5).

Last two structures are quite similar, but the difference in the asymmetric units (one is monomer and the other is a dimer) involve a little difference in chains construction. In fact comparing the two unit cells is evident that in the second one there is staggering of the two parts that compose the asymmetric unit, this staggering involve the difference in the chains.

In the first one all eight-member rings are all equal, in the second chain there are two types of eight-member rings, alternating between them.

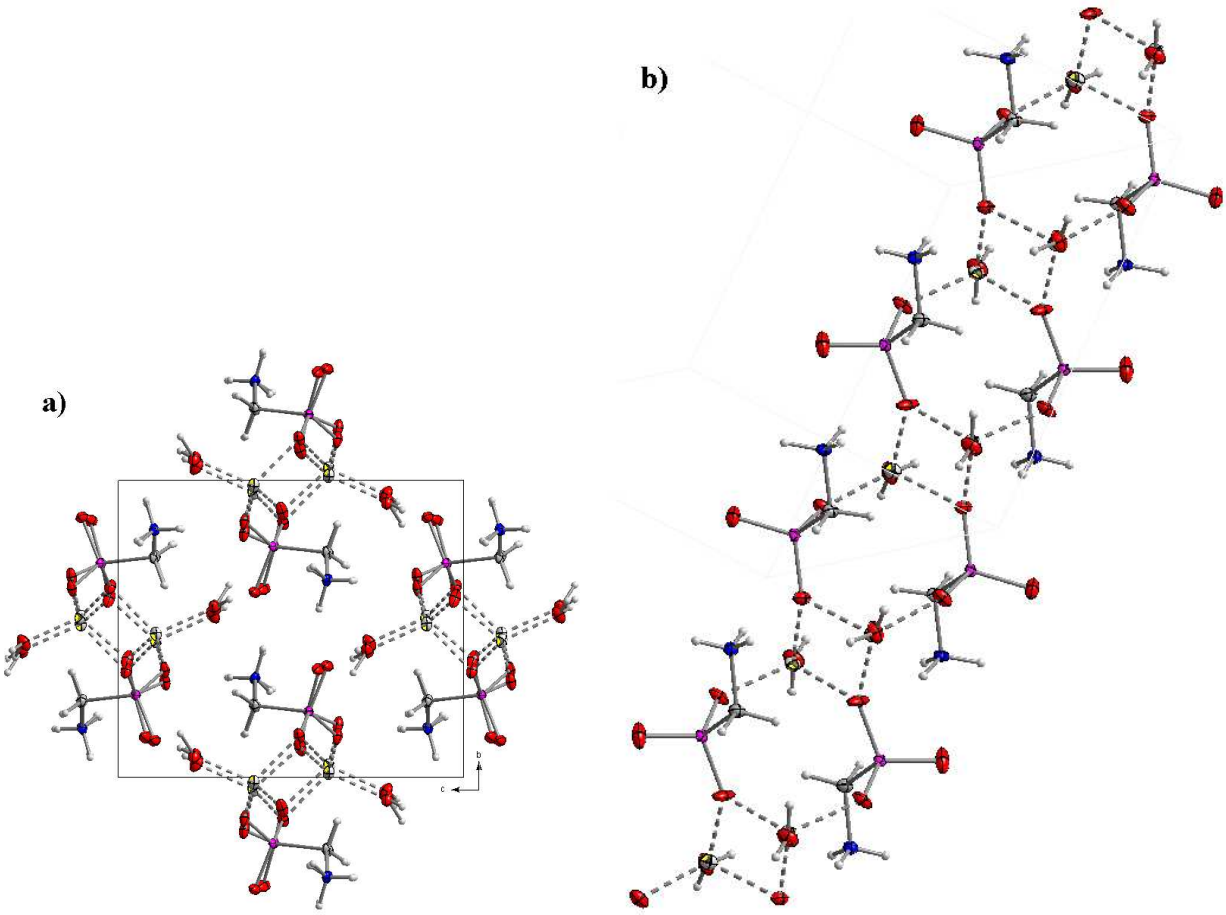

Figure 13.5 Structure of AMP+Li_2CO_3. a) Unit cell locking along the a axis, where is evident the staggering of two parts that compose the asymmetric unit; b) chain, where is clear the presence of two types of eight-member rings.

13.3 Conclusion

In conclusion we have reported the synthesis of three different structures for the complex formed by aminomethylphosphonic acid and lithium compounds. From these studies we can affirmed that the principals factors that driven the formation of the structure are the kind of lithium compound and the crystallization method, while the molar ratio between two reagents not influenced the outcome of the reaction.

13.3 Experimental section

13.3.1 General

Standard glassware was used for the reaction. The water was deionized. All reaction was carried out in atmospheric condition. Lithium compounds, was commercially available and used without further purification. Aminomethylphosphonic acid was synthesized by Hägele, in according with methodology reported in literature.
Crystallographic experiments were performed with an Oxford Xcalibur3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-Kα radiation (λ = 0.71071 Å). Data collection was performed with the Crysalis CCD software; Crysalis RED software was used for data reduction. Absorption correction by using the SCALE3 ABSPACK multiscan method was applied. The structures were solved with SHELXS-97, refined with SHELXL-97 and finally checked by using PLATON.

13.4.2. AMP+ LiOH 1/1

23 mg (0.25 mmol) of aminomethylphosphonic acid and 6 mg of LiOH were dissolved in 3 mL of water in an open vial and heating to 70 °C, after one hour two reagents were completely dissolved, the reaction mixture was put to crystallize at room temperature. The crystallization occurs by solvent evaporation. Crystal was separated by filtration. Crystal data are reported in table 13.1. Selected bond lengths and bond angles are reported in table 13.2.

14.3.3 AMP+ LiOH 2/1

23 mg (0.25 mmol) of aminomethylphosphonic acid and 12 mg of LiOH were dissolved in 3 mL of water in an open vial and heating to 70 °C, after one hour two reagents were completely dissolved, the reaction mixture was put to crystallize at room temperature. The crystallization occurs by solvent evaporation. Crystal was separated by filtration.

14.4.4 AMP+ LiOH 1/1 crystallization with Methanol

23 mg (0.25 mmol) of aminomethylphosphonic acid and 6 mg of LiOH were dissolved in 3 mL of water in an open vial and heating to 70 °C, after dissolution, the vial with reaction mixture, was put in a wider vial, which were placed 3 mL of methanol. The wider vial was stoppered. The crystallization occurs by slowly evaporation of methanol, which mixes with the water into the

smaller vial, causing a decrease in polarity, thus favouring the crystallization. Crystal was separated by filtration. Crystal data are reported in table 13.1. Selected bond lengths and bond angles are reported in table 13.2.

13.4.5 AMP+ Li_2CO_3 1/1

46 mg (0.5 mmol) of aminomethylphosphonic acid and 18.5 mg of Li_2CO_3 were dissolved in 2 mL of water in an open vial, after dissolution of the reagents the reaction mixture was put to crystallize at room temperature. The crystallization occurs by solvent evaporation. Crystal was separated by filtration. Crystal data are reported in table 13.1. Selected bond lengths and bond angles are reported in table 13.2.

Tabella 13.1 Crystallographic data

	AMP+LiOH 1/1	**AMP+LiOH 1/1 (CH3OH)**	**AMP+Li_2CO_3 1/1**
Empirical formula	CH_7NO_4PLi	CH_7NO_4PLi	$C_2H_{14}N_2O_8P_2Li_2$
Formula weight	135,027	135,027	270,055
T (K)	173	173	173
Crystal size (mm)	0.30x0.30x0.10	0.15x0.20x0.13	0.21x0.10x0.11
Crystal description	colourless block	colourless block	colourless block
Space group	$P2_1/n$	$P2_1/n$	$P2_1/c$
Crystal system	Monoclinic	Monoclinic	Monoclinic
a (Å)	5.7712(2)	5.1407(3)	10.2884(5)
b (Å)	9.3542(3)	9.1292(5)	9.1149(4)
c (Å)	9.4656(4)	10.9184(6)	10.9223(4)
α (°)	90.000	90.000	90.000
β (°)	107.591(4)	103.414(5)	103.765(4)
γ (°)	90.000	90.000	90.000
V (Å3)	487.10(3)	498.43(5)	994.85(8)
Z	5	5	11
ρ calcd	1.380	1.348	1.486
μ [mm–1]	0.489	0.478	0.527
***F*(000)**	200.0	200.0	440.0
θ range [°]	4.30–24.99	4.44 –24.99	4.45–25.00
Index ranges	$-6 \le h \le 6$	$-6 \le h \le 6$	$-10 \le h \le 12$
	$-11 \le k \le 11$	$-10 \le k \le 10$	$-10 \le k \le 10$
	$-11 \le l \le 11$	$-12 \le l \le 12$	$-12 \le l \le 12$
Reflns. collected	6252	6210	4578
Reflns. obsd	758	758	1163
Reflns. unique	851 (R_{int} 0.0267)	866 (R_{int} 0.0320)	1739 (R_{int} 0.0331)
R_1, wR_2 (2σ data)	0.0229 ,0.0647	0.0408, 0.1061	0.0349, 0.0792
R_1, wR_2 (all data)	0.0260, 0.0660	0.0469, 0.1092	0.0538, 0.0823
GOOF on F_2	1.161	1.101	1.078
Peak/hole [eÅ–3]	0.344/-0.362	0.759/-0.802	0.701/-0.316

Table 13.2. Bond lengths(Å), Bond angles (°)

	AMP+LiOH 1/1	AMP+LiOH 1/1 (CH3OH)	AMP+Li2CO3 1/1
Bond lengths			
Li(1) – O(1)	1.961(2)	1.988(6)	1.948(5)
Li(1) – O(4)	1.981(2)	1.949(6)	1.935(6)
P(1) – O(1)	1.5332(12)	1.494(2)	1.510(2)
P(1) – O(2)	1.5085(12)	1.501(3)	1.513(2)
P(1) – O(3)	1.5217(12)	1.496(2)	1.509(2)
P(1) – C(1)	1.8161(16)	1.819(3)	1.817(3)
C(1) – N(1)	1.490(2)	1.481(4)	1.484(4)
Li(2) – O(5)			1.898(5)
Li(2) – O(8)			1.973(6)
P(2) – O(5)			1.510(2)
P(2) – O(6)			1.5106(19)
P(2) – O(7)			1.520(2)
P(2) – C(2)			1.816(3)
C(2) – N(2)			1.472(4)
Bond angles			
O(4) – Li(1) – O(1)	109.13(14)	112.0(3)	103.8(2)
Li(1) – O(1) – P(1)	118.27(10)	127.2(2)	129.9(2)
O(1) – P(1) – O(2)	113.40(7)	112.3(2)	113.89(12)
O(1) – P(1) – O(3)	11.7786)	114.47(17)	113.59(13)
O(1) – P(1) – C(1)	104.32(7)	103.23(14)	105.63(13)
O(2) – P(1) – O(3)	112.67(7)	111.5(2)	111.45(13)
O(2) – P(1) – C(1)	107.48(7)	107.79(15)	103.84(13)
O(3) – P(1) – C(1)	106.52(7)	106.77(14)	107.56(14)
P(1) – C(1) – N(1)	11.24(11)	114.6(2)	114.3(2)
O(1) – Li(1) – O(6)			108.3(3)
O(4) – Li(1) – O(6)			121.5(3)
O(8) – Li(2) – O(1)			97.9(2)
Li(2) – O(1) – P(2)			136.7(2)
O(1) – P(1) – O(2)			114.44(12)
O(1) – P(1) – O(3)			111.23(12)
O(1) – P(1) – C(1)			107.42(13)

O(2) – P(1) – O(3)	112.96(12)
O(2) – P(1) – C(1)	102.44(13)
O(3) – P(1) – C(1)	107.60(13)
P(1) – C(1) – N(1)	114.6(2)

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