CHAPTER 1

1. INTRODUCTION

1.1 General Background

Phosphorus is an unusual chemical element. In the pure form it can burst into flames spontaneously but is also used in some of the best flame-retarding agents.[1] Tiny amounts of phosphorus play a vital role in all living processes in plants and animals.[2,3] Gorenstein et.al.[4] refers to DNA, the genetic tape that guides the reproduction of all species, as the ultimate phosphorus polymer. The essential functions of phosphorus are performed in the form of phosphate esters and diesters[5]. The predominant example of a naturally occurring phosphorus-carbon compound, is 2-aminoethylphosphonic acid, **A** which was isolated from certain protozoa (**Figure 1.1**).

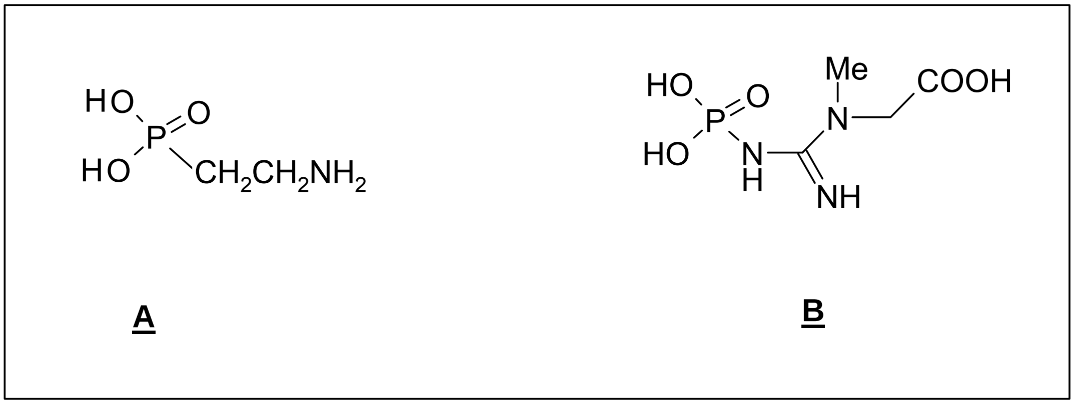
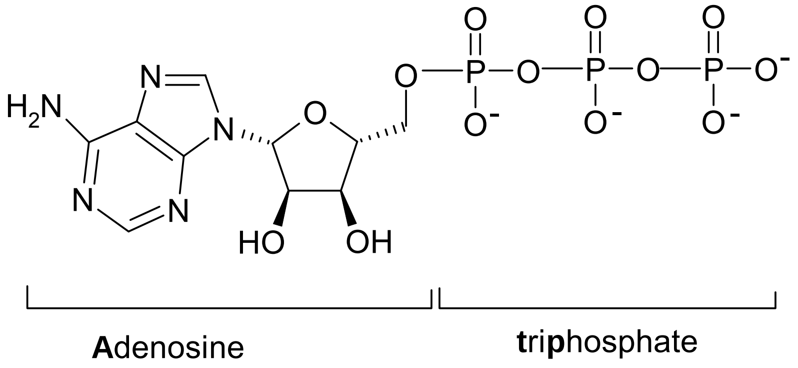


Figure 1.1 Structures of 2-aminoethylphosphonic acid, **A** and phosphocreatine, **B**.

Phosphocreatine **B** is an essential phosphorus-nitrogen compound and this bond may be the reason for its usefulness as a stored form of phosphate[6]. This compound is held in reserve as a reagent for the emergency regeneration of adenosine triphosphate (ATP) **C** (**Figure1.2**). ATP supplies energy for all metabolic pathways important in living organisms.



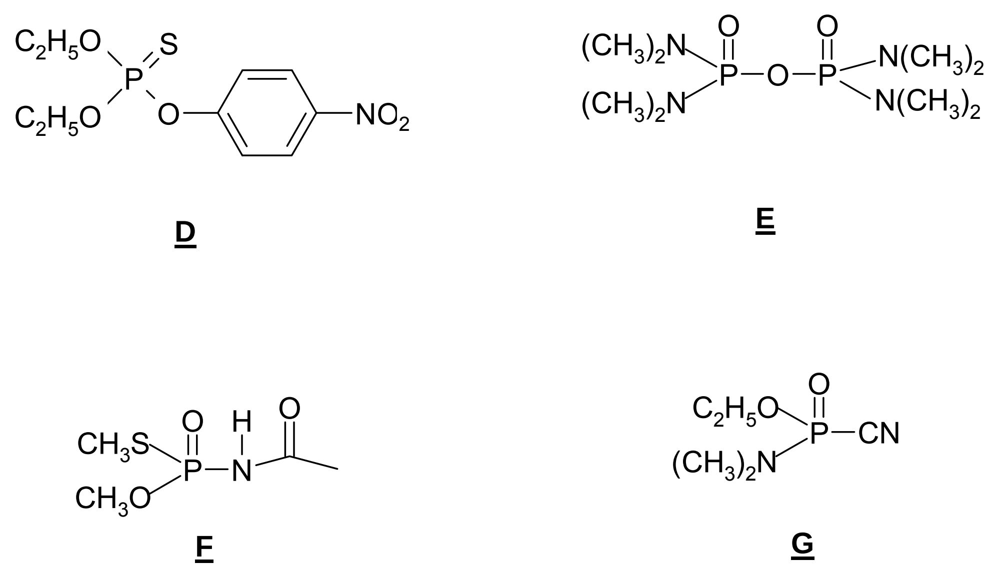
C

Figure 1.2 Structure of adenosine triphosphate (ATP).

The fact that organophosphorus compounds can form substances with the coordination number of phosphorus ranging from 1 to 6 made a lot of questions arise regarding the stability and reactivity of these compounds. The academic interest in phosphorus compounds made the knowledge of phosphorus chemistry expand enormously since 1960 and the number of phosphorus compounds increased considerably[7], with diverse practical applications.

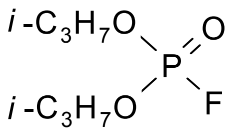
Modern investigations of organophosphorus compounds started in 1932 with the preparation of the dimethyl and diethyl phosphorofluoridates[8]. The statement that inhalation of these compounds caused a persistent choking sensation and blurred vision made Schrader[9] explore this class of compounds for insecticidal activity. This study resulted in preparing the well-known insecticide Parathion[10] (O,O-diethyl O-(4-nitrophenyl)-phosphorothioate) **D**. Further examples are octamethylpyrophosphoramide (Shradan) **E** and N-acetyl-O,S-dimethylphosphoramidothioate (Orthene) **F** which are systemic and contact insecticides respectively. Prior to the Second World War Schrader established the extremely high toxicity of an organophosphorus compound, O-ethyl *N,N*-dimethylphosphoramidocyanidate (Tabun)[11] **G** that became the first of the lethal organophosphorus chemical warfare agents. Tabun is a nerve gas, which causes death by blocking nerve function activity.

McCombie and Saunders[12] synthesized the chemical warfare agent diisopropyl phosphorofluoridate (DFP) **H**, which was the organophosphorus compound studied most extensively by British and American scientists.



D **E** **F** **G**

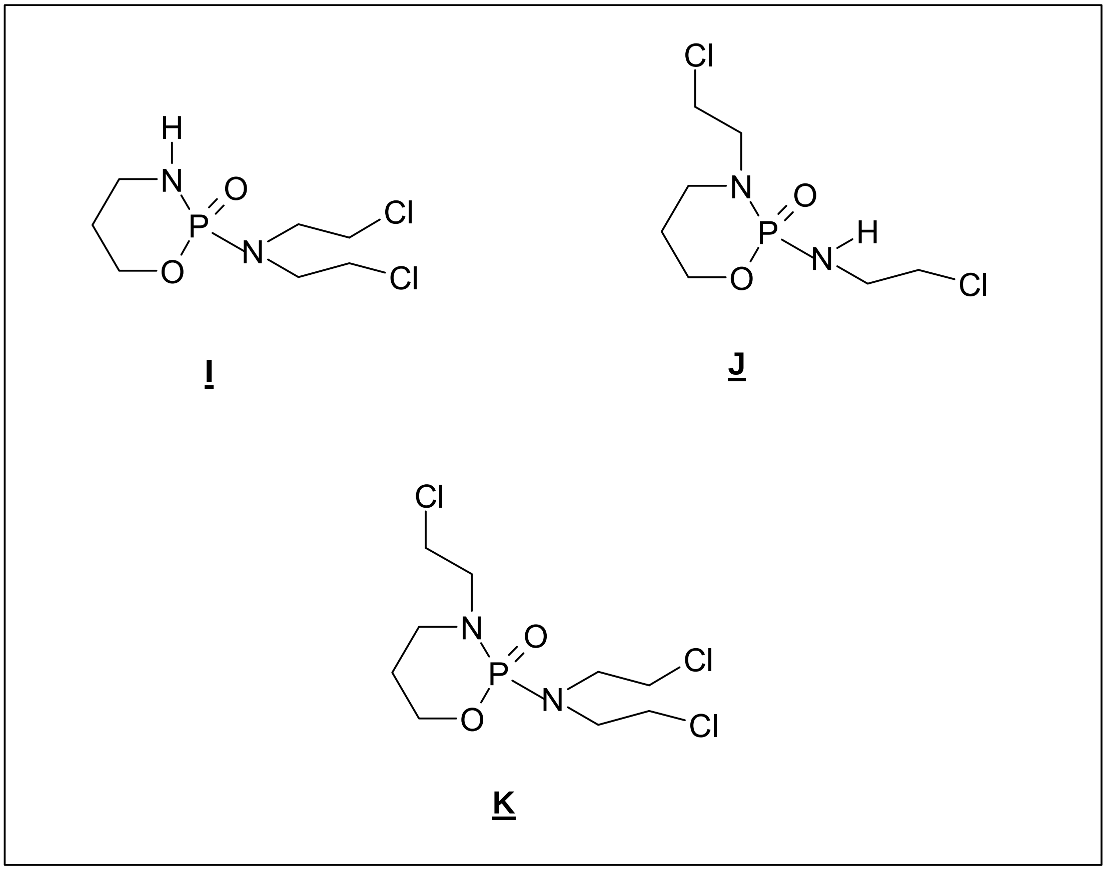
Figure 1.3. Structures of Parathion **D**, Shradan **E**, Orthene **F** and Tabun **G**.



H

Figure 1.4 Diisopropyl phosphorofluoridate (DFP).

The family of phosphorylated nitrogen mustards, i.e. compounds containing the *bis*-(2-chloroethyl)amino group, are known to be highly effective alkylating agents with respect to a variety of nucleophilic centers, which find application in anti-tumor chemotherapy[13,14,15]. The alkylating mechanism of these compounds[16,17,18] like Cyclophosphamide **I**, Ifosphamide **J** and Trofosphamide **K**, (**Figure 1.5**) has been thoroughly investigated and is well documented.



I

J

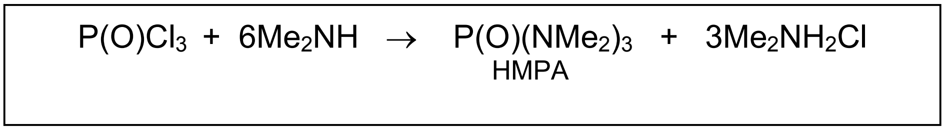
K

Figure 1.5 Structures of Cyclophosphamide **I**, Ifosphosphamide **J** and Trofosphamide **K**.

Compounds containing a nitrogen atom bonded to phosphorus represent an important class of organophosphorus compounds. The field of phosphorus-nitrogen chemistry attracted a lot of attention as phosphorus and nitrogen produce an interesting bonding system. The amine and amide derivatives of four-coordinate pentavalent phosphorus have a formal σ P-N single bond. However this simple bond can have an element of extra bonding, involving a

$2p(N)\rightarrow 3d(P)\pi$ donor system. When the bond distance between phosphorus and nitrogen is relatively short, the nitrogen is sp^3 hybridized (tetrahedral geometry), donating the lone pair of electrons to an empty 3d orbital of phosphorus. As the bond distance increases, the nitrogen loses some of its '*s*' character to approach 'p^3' character. The nitrogen in this 'unhybridized' state has an ideal pyramidal geometry with the lone pair of electrons occupying the 2*s* atomic orbital of nitrogen. This change in hybridization has a direct effect on the ^{31}P NMR chemical shift. This phenomenon is discussed later in this chapter. The degree of π bonding with phosphorus also reflects the basicity of the nitrogen atom.

Most of the interest in phosphorus-nitrogen chemistry is centered on the phosphoryl derivatives. One such derivative is hexamethylphosphoramide (HMPA) that seems to be the most used compound in this series. HMPA is a good polar aprotic non-aqueous solvent, which is prepared from $P(O)Cl_3$ and an excess of dimethylamine (**Scheme 1.1**).

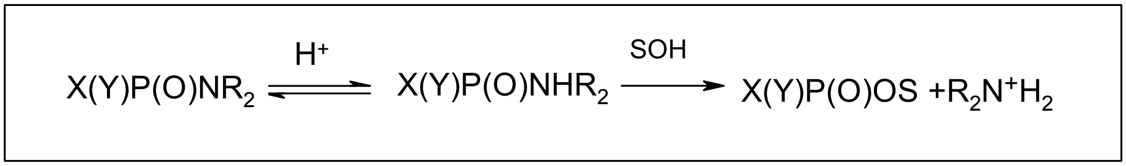


$$P(O)Cl_3 + 6Me_2NH \rightarrow \underset{\text{HMPA}}{P(O)(NMe_2)_3} + 3Me_2NH_2Cl$$

Scheme 1.1 Preparation of hexamethylphosphoramide (HMPA).

The same reaction applies with the use of $P(S)Cl_3$ and almost any amine. This type of reaction was the starting point for the synthesis of almost all compounds discussed in this project.

Systems containing the phosphoramidate function P(O)N have been the subject of research in our laboratories for many years. The physical and chemical characteristics of the phosphoramidates have been investigated.[19,20,21] Many features of the P-N bonding in this system have been explored e.g. the nucleophilic cleavage of the P-N bond[22,23] and the nucleophilicity of the P(O)N function[24]. The remarkably facile fission of the P-N bond under mildly acidic conditions found synthetic application in preparation of chiral organophosphorus compounds[25,26] as well as in the modification of the Gabriel procedure of preparing aliphatic amines.[27] It was demonstrated that phosphoramidates solvolyze via the N-protonated reactive intermediates, which then undergo bimolecular nucleophilic attack by a solvent molecule[28,29] (**Scheme 1.2**).



$$X(Y)P(O)NR_2 \xrightleftharpoons{H^+} X(Y)P(O)NHR_2 \xrightarrow{SOH} X(Y)P(O)OS + R_2N^+H_2$$

Scheme 1.2 Protonation reaction of the phosphoramidates.

The intramolecular reactivity of a series of phosphorotriamidates with the general structure, $(RNH)_2P(O)NHCH_2CH_2Cl$, was studied.[30] Under strongly basic conditions, the *N*-alkyl derivatives (R=Me, $PhCH_2$) underwent intramolecular displacement of the chloride yielding the *N*-phosphorylated aziridine **L** (**Figure 1.6**), as the exclusive cyclization product.

For *N*-aryl derivatives (R=Ar), both the aziridine **L** and the 1,3,2-diaza-phospholidine products **L’** could be obtained in comparable yields.

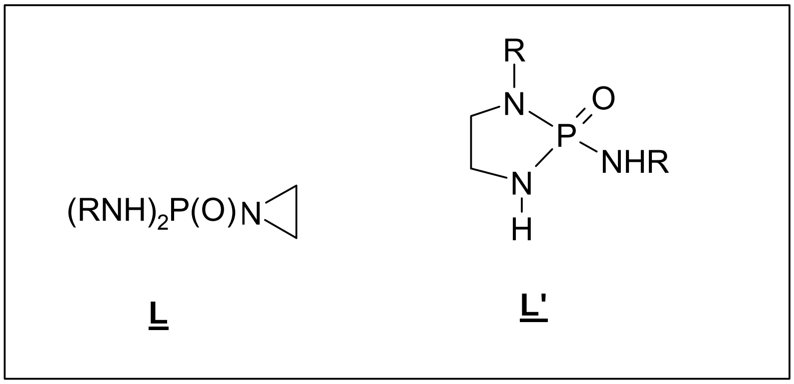


Figure 1.6 Aziridine and 1,3,2-diazaphospholidine derivatives.

The *N*-aromatic cyclic products are mutually interconvertible: 1,3,2-diaza-phospholidines rearrange to the corresponding aziridines upon treatment with base, while bromide ion catalyzes the reverse isomerization.

The chemistry of the phosphorylated nitrogen mustards was further investigated by determining the effect of increasing the nucleophilicity of the phosphate moiety, by incorporation of a second nitrogen at the phosphoryl center[31], on the stability of the system.

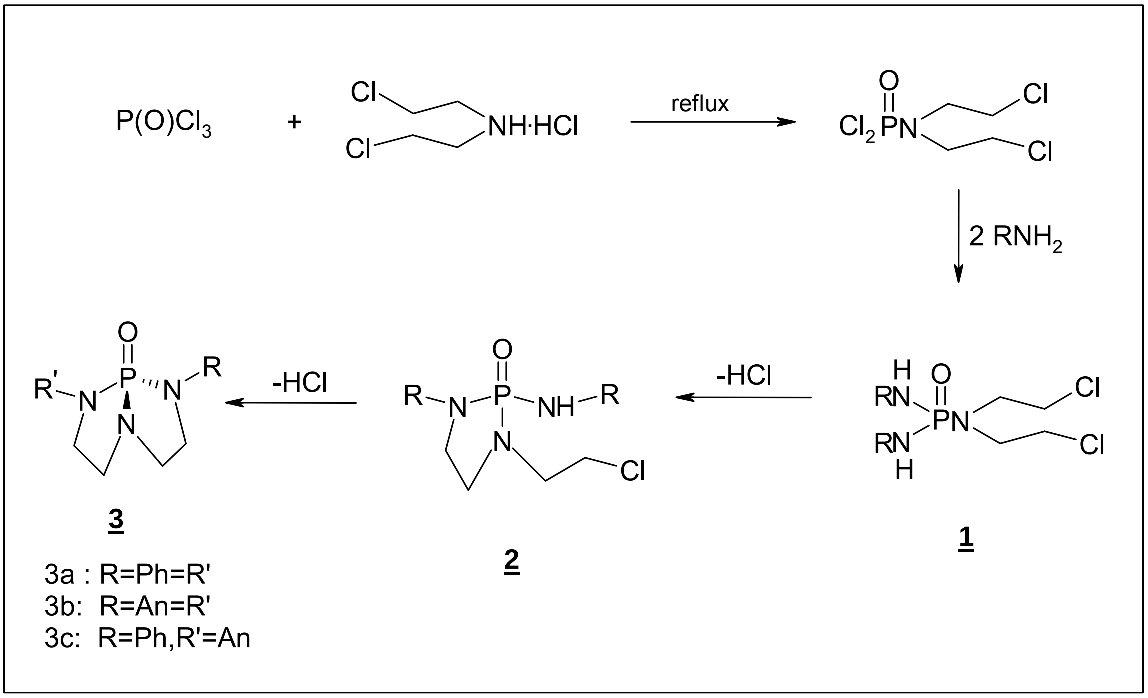
Those preliminary results[30,31] indicated that the *N*-phosphorylated nitrogen mustards have rich and diverse chemistry, and the potential of those systems had become a major research field in our laboratory.

^{31}P and ^{15}N NMR spectra of eleven cyclic and non-cyclic, closely related phosphoramides were measured and the structures demonstrated a correlation between the bond angles at nitrogen, the ^{15}N NMR chemical shift and the $^{1}J(P,N)$ coupling constants[32].

With ^{15}N NMR spectroscopy it was possible to distinguish between the *exo*- and *endo*-cyclic nitrogens in the monocyclic triamides. ^{15}N NMR chemical shift values are good indication of the relative basicities of nitrogen atoms in phosphoramidates. This was demonstrated by the rates of acid catalyzed cleavage of the P-N bond in the cyclic substrates.

It was also observed that some phosphoric amides containing a chiral phosphorus atom can act as chiral recognition agents with respect to optically active compounds.[33] By acting as both, donors and acceptors for hydrogen bonding,[34] they formed diastereomeric hydrogen bonded complexes with optically active carboxylic and sulphonic acids.

The synthetic potential of the phosphorylated nitrogen mustards was explored by utilizing the two 2-chloroethyl chains of the mustard group to prepare a novel bicyclic system **3** (**Scheme 1.3**). A series of phosphotriamidates were prepared[35] which all have the essential structural feature, the $-N(CH_2CH_2Cl)_2$ group, attached to phosphorus.



Scheme 1.3 Reaction pathway to prepare the bicyclic compound **3**. An = 4-$CH_3OC_6H_4$.

The preparation of the noncyclic triamides **1** involves three subsequent nucleophilic displacement reactions at the phosphoryl center. The order of the introduction of the nucleophiles is important. The best yields were obtained when the mustard function was introduced first.

The bicyclic derivatives **3** were prepared from the non-cyclic derivative **1** via two successive base promoted cyclization reactions. The deprotonation of the amide hydrogens is followed by the intramolecular displacements of the β-chloro atom of the N-mustard function. The amide hydrogens of the noncyclic triamidate **1** are more acidic than the amide hydrogen of the monocyclic compound **2**, causing the first cyclization to take place more easily. For the second cyclization a stronger base was needed.

Phosphorus and nitrogen form part of the heterocyclic ring in the bicyclic compound. This arrangement of atoms, consisting of two fused rings with the phosphorus and one nitrogen in the bridgehead positions, and the phosphorus attached to another two nitrogen atoms, represents a completely new heterocyclic system. The compounds with aromatic substituents on nitrogen atoms are stable crystalline compounds and were studied in detail.

The physical characteristics of the phosphoramidates e.g. the bond angles and bond distances (obtained from X-ray crystallographic data) were correlated with ^{31}P NMR data of a series of triamidates.[36] This correlation clearly indicated that the ^{31}P NMR chemical shift depends on the bond angles as well as the hybridization of the nitrogen atoms bonded to phosphorus. The noncyclic **1**, monocyclic **2**, bicyclic **3** and tricyclic **4** compounds in this series are characterized by specific values of ^{31}P NMR chemical shifts (δ_P).

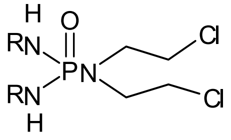
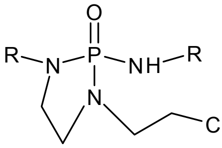
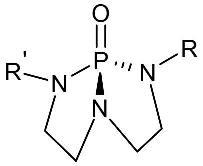
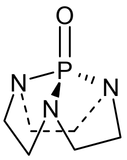
Triamidate	**Structure**	**δ_P Value**
Non-cyclic **1** R=Ph		~ 5 ppm
Monocyclic **2** R=Ph		~ 12 ppm
Bicyclic **3** R=Ph		~ 33 ppm
Tricyclic **4**		~ 98 ppm

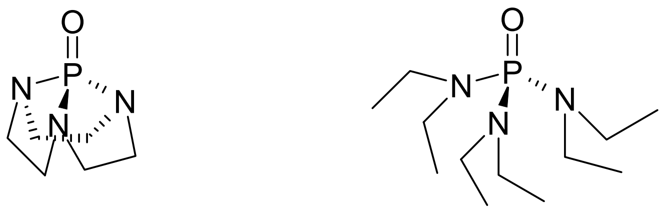
Table 1.1 ^{31}P NMR chemical shifts of the triamidates series.

With the incorporation of each ring (from 0 to 3), there is a regular downfield shift in the ^{31}P NMR chemical shift. (**Table 1.1**). The typical range of the δ_P values for compounds with the phosphoryl function bonded to three nitrogen atoms[37] lies between 5 and 33 ppm. Compound **4** however, has a δ_P value of 98 ppm.

The ^{31}P chemical shift differences, $\Delta\delta_P$, are described by equation 1.2[38], where $\Delta\chi_x$ is the difference in the electronegativity in the P-N bond, Δn_π the change in the π overlap and $\Delta\theta$ the change in the N-P-N bond angle. *C, k* and *A* are constants.

$$\Delta\delta_P = -C\,\Delta\chi_x + k\,\Delta n_\pi + A\,\Delta\theta$$ **Equation 1. 1**

With the atoms bonded to phosphorus being constant and the substitution on nitrogen also the same in **1**, **2** and **3**, it can be deduced that the deshielding effect does not result from electronegativity differences, but from changes in the geometry of the P-N tetrahedron. This change in δ_P is a result of the change in geometry of the molecule, which leads to the change in bond angles This in turn causes changes in the hybridization of the nitrogen atoms. In the series **1**→**4**, the N-P-N bond angles decrease while the P-N bond distance increases. When **4** is compared with the non-cyclic hexaethylphosphoric triamide **4”**, (δ_P 23.3) any differences in polar effects of substituents can be ignored and the dramatic



4

$\delta_P = 98$

4''

$\delta_P = 23.3$

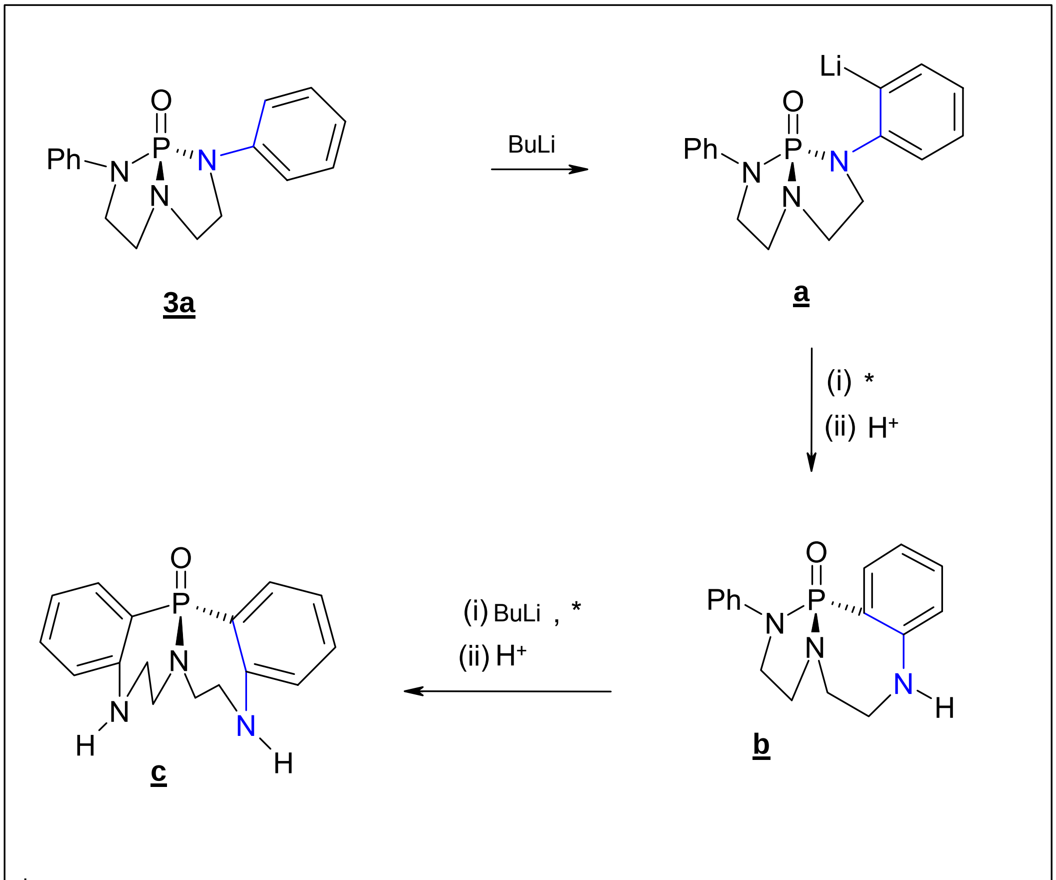
Figure 1.7. Structures of 10-oxo-10-phospha-1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]-decane, **4** and hexaethylphosphoric triamide, **4’’**.

deshielding effect of 74.7 ppm (difference between δ_P values of **4** and **4”**) must solely reflect the difference in geometry.

The δ_P values of compounds **1**, **2**, **3** and **4** are related to the average values of the three N-P-N bond angles present in each molecule, demonstrating that variations in geometry can lead to formidable changes in shielding parameters at the phosphoryl center. This observed variations in the P-N bond characteristics should be reflected by significant differences in the chemical behavior of the individual classes of the new bicyclic system **3.**

The bicyclic system **3** revealed an interesting chemistry, which stimulated the synthesis of new heterocyclic compounds containing nitrogen and phosphorus in the ring skeleton. Metallation induced migration of phosphorus from nitrogen to carbon yields new types of cyclic phosphonic and phosphinic amides[39]. (**Scheme 1.4**)

The N⇒C migration of phosphorus in **3a** involves three steps: lithiation of the *ortho*-carbon in the N-Ar group, 1,3-phosphorus shift driven by the formation of a strong P-C bond together with the change of the N-Li bonding, and, finally, quenching of the N-lithiated amide function by a proton donor. In this way new bicyclic systems containing fused five- and seven-, as well as two seven-membered rings (**a**,**b** and **c**) have been prepared.

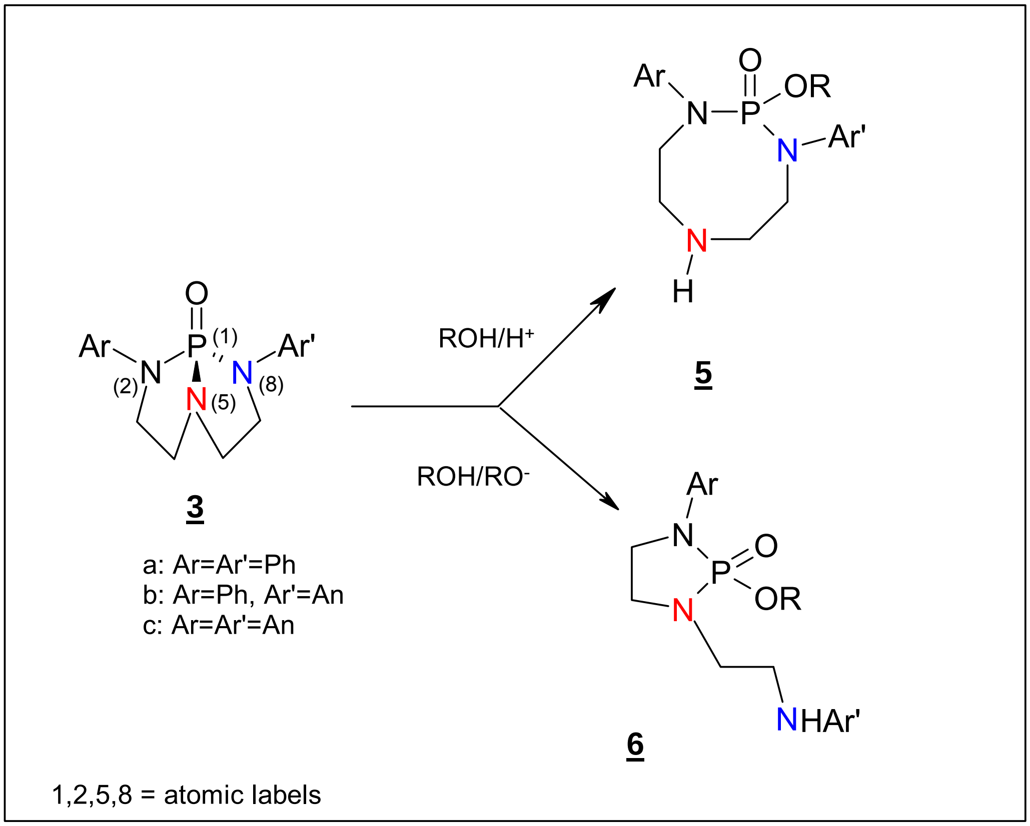


* Migration of P from N to C

Scheme 1.4 Metallation induced migration of Phosphorus from Nitrogen to Carbon.

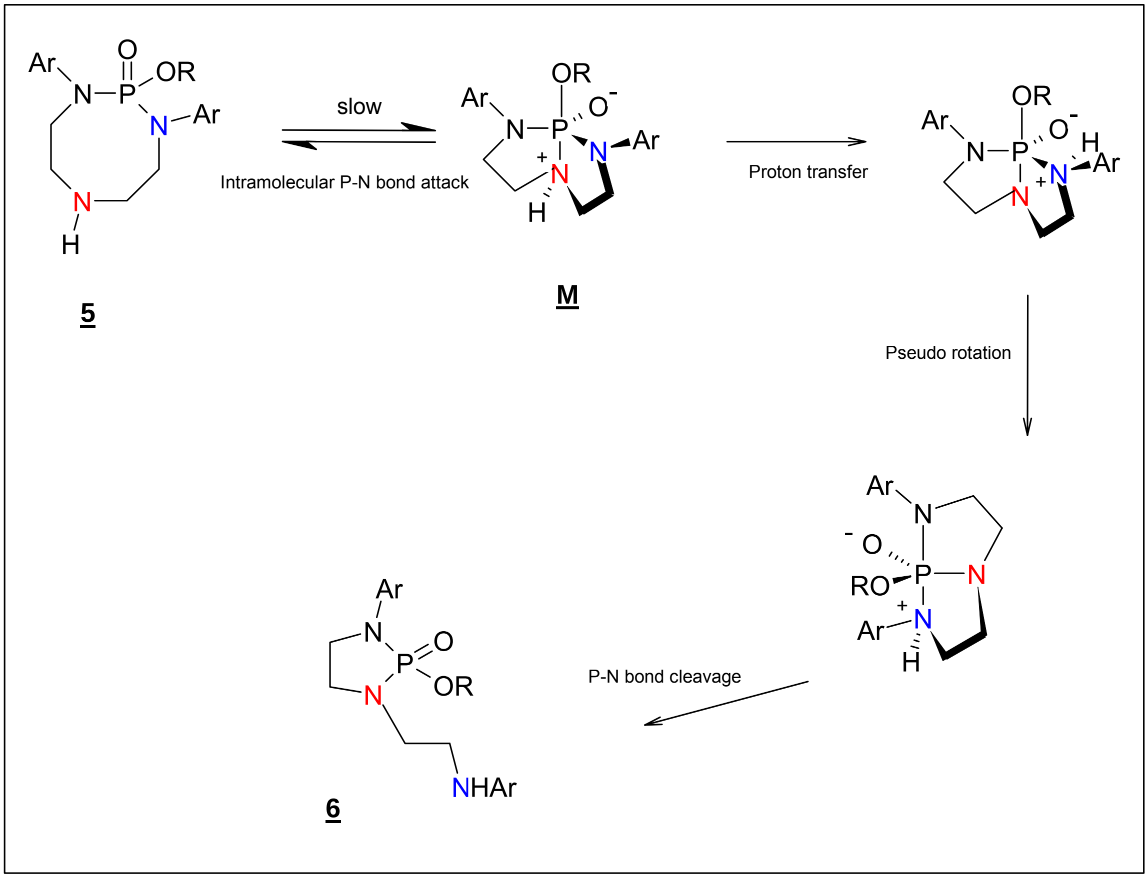
The nucleophilic cleavage of one of the P-N bonds in the bicyclic system **3** leads to a novel eight-membered heterocyclic system **5** or to the 1,3,2-diaza-phospholidine derivative **6**.[40] (**Scheme 1.5**)

Quantitative and regiospecific cleavage of the "internal' P-N(5) bond was obtained when **3** was treated with an alcohol (R= Me, Et), containing one mole equivalent of HCl. This reaction yielded the hydrochloride salt of the corresponding triazaphosphacyclooctane **5.** The free base of **5** was obtained by neutralization. The regioselectivity of the reaction can be explained in terms of the mechanism of the acid-catalyzed P-N bond cleavage in phosphoric amides, established by Rahil and Haake.[41] According to that mechanism, the first step involves the N-protonation, followed by the direct displacement of the amine by the nucleophilic reagent. In **3a** (R=Ph) the bridgehead nitrogen, N(5), substituted by two alkyl groups, should be significantly more basic than two aryl-substituted nitrogens, thus the substrate should be exclusively activated for the P-N(bridgehead) bond cleavage. ^{15}N NMR studies confirmed the *p*^{3} character of this nitrogen suggesting higher basicity of the bridgehead nitrogen, N(5). Stereoelectronic effects also play a role in the selectivity of the reaction. In the transition state (the P(V) intermediate) of the substitution the N(5) atom is in the apical position which is the most favored location for the leaving group in the trigonal bipyramid structure.



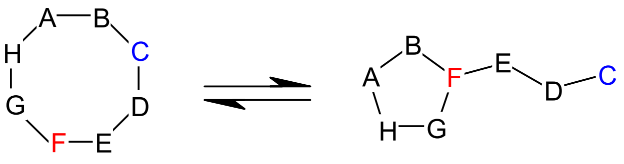
Scheme 1.5 Acid and Base catalyzed cleavage of the P-N bond in **3**.

The eight-membered ring compound **5a** undergoes slow and spontaneous change yielding another P-containing compound **6a**. According to the available data, a mechanism is proposed for this isomerization which involves the rate-determining intramolecular 1,5-nucleophilic attack of the amine nitrogen at the phosphoryl center, resulting in the P(V) intermediate **M** (**Scheme 1.6**), which then undergoes fast proton transfer, pseudorotation, and product determining cleavage of the P-N(8) bond. This mechanism is supported by the structural characteristics (short distance between the N(5) and P atoms) of the *N*-benzoyl derivative of **5a**.



Scheme 1.6 Proposed mechanism of the rearrangement of **5** to **6**.

For the hydrolysis of medium ring phosphate esters, a similar mechanism was postulated. In those cases[42,43] the transannular N→P interaction in an eight membered heterocyclic system catalyzes the hydrolysis, but the rings stay intact. However for **5a** there is a change in the molecular skeleton. (**Scheme 1.7**) The letters in the scheme are used to demonstrate the ring contraction in this rearrangement where **i** and **ii** represent the 2,5,8-triaza-1λ^5-phosphabicyclooctane and the 3-substituted 1,3,2λ^5-diazaphospholidine system, respectively. A new bond is formed between atoms B and F and the B-C bond is broken. To our knowledge, this was the first reported case of a rearrangement of this type.



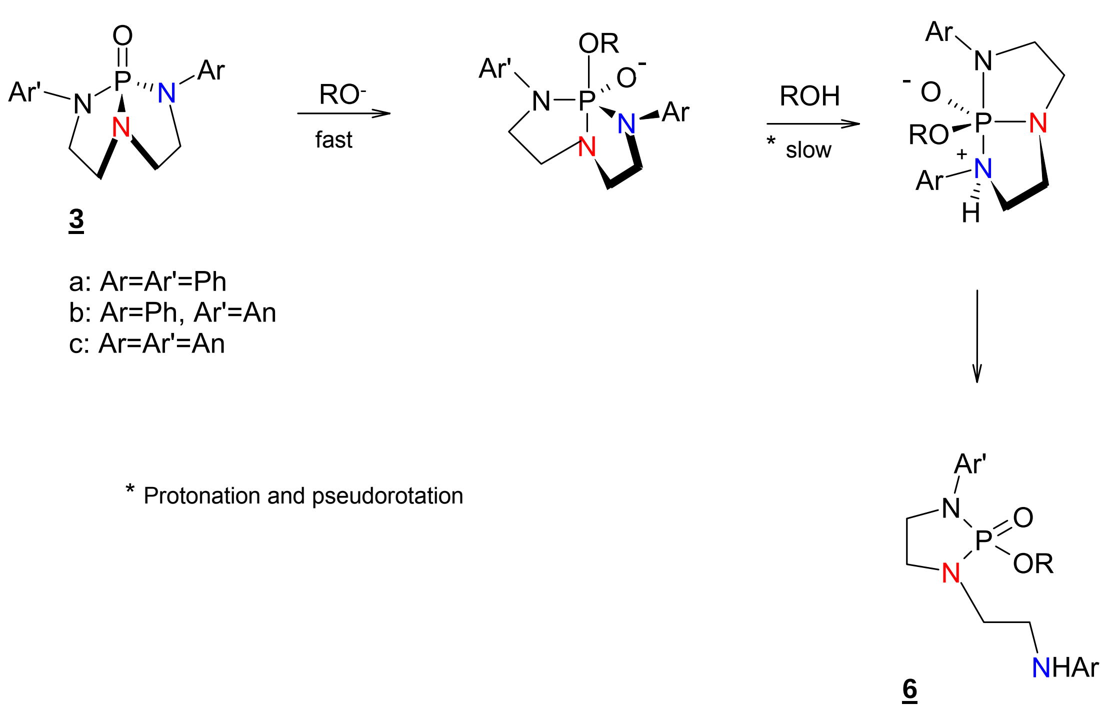
i **ii**

Scheme 1.7 Ring contraction in the rearrangement reaction.

Compounds **5** are stable in the form of their ammonium salts or as the N(5)-acyl derivatives. The nature of the nucleophilic group introduced at the phosphoryl center in the ring-opening reaction, determines the stability and the behavior of the neutral products **5**[44].

Basic alcoholysis (RO^-/ROH) of the bicyclic substrate **3** led to the formation of the five membered ring product, **6** as a result of the nucleophilic cleavage of the P-N-Ph bond. The same behavior was observed for another N-aryl substrate where R=4-$MeOC_6H_4$. The products **6** could be prepared therefore either by direct alcoholysis of **3** or via the rearrangement of **5**.

The mechanism of the base-catalyzed alcoholysis of **3** is much less clear. In the absence of activation of N(5) via protonation, the leaving ability of the departing nitrogen atom determines the regioselectivity of the P-N bond cleavage. (**Scheme 1.8**)



3

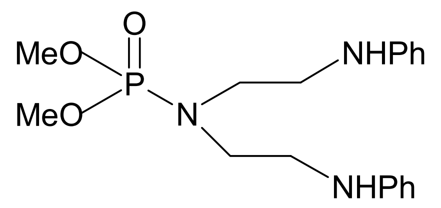
a: Ar=Ar'=Ph
b: Ar=Ph, Ar'=An
c: Ar=Ar'=An

* Protonation and pseudorotation

6

Scheme 1.8 Mechanism of the base catalyzed reaction.

With excess of MeO- the five membered product **6a** undergoes further opening of the second 1,3,2λ^5-diazaphospholidine ring to give dimethyl di(2-phenyl-aminoethyl)phosphoramidate **7a**.



7a

Figure 1.8 Dimethyl di(2-phenyl-aminoethyl)phosphoramidate **7a**.

The **5**→**6** rearrangement indicates greater thermodynamic stability of the five-membered ring **6**. In the further part of this work the results are reported of the attempts to demonstrate the thermodynamic reasons for the rearrangement using the Molecular Modelling (MM) approach, as well as to show the concerted nature of the reaction.

The ring substituents play a role in both reactions: in the regioselectivity of the P-N bond cleavage by nucleophiles, as well as in the rearrangement reaction. For the base catalyzed substitution in **3a**, the electron-donating substituents in the *N*-Ar function in **5** *increase* the rate of reaction. When R=R'=4-MeOC_6H_4 (**3b**), the bond cleavage was about 2.5 times faster than for **3a**. The mixed substrate **3c** (R=4-MeOC_6H_4; R'=Ph) showed preference for cleavage of the P-NAn bond over the P-NPh bond. The higher basicity of the leaving amine facilitates in this case the proton transfer necessary for the departure of the leaving group.

The opposite was observed for the rearrangement reaction - the bis-*N*-anisydyl substrate **3b** proved to be the least reactive. This can be explained according to the different proposed mechanisms for the two processes. In the base catalyzed reaction, the P-O bond formation with a strong nucleophile (EtO^-) is fast, but the proton-assisted cleavage of the P-N(2) bond is rate determining. The more basic *N*-*p*-anisyl function in **3b** makes the intermediate more reactive in the second, dissociative step of the reaction.

In the rearrangement, on the other hand, the less electrondonating phenyl substituents (**3a** and **3c**) make the phosphorus atom more electrophilic thus making **3a** more reactive in the rearrangement. The rate of the rearrangement is determined by the rate of the N(5)-P bond formation, resulting in the P(V) intermediate, which then undergoes fast proton transfer and product determining cleavage of the P-N(2) bond.

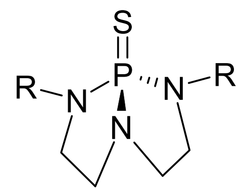
With the molecular rearrangement (**5**→**6**) being reasonably well understood for the *N,N*'-diaryl substituted substrates (**3a**, **3b** and **3c**), it was decided to expand our studies of the bicyclic system **3** to other derivatives with different substitution of the nitrogen atoms.

1.2 Objectives

Against the described background of the previously accumulated results, the objectives of this study were to:

- synthesize some *N*-alkyl derivatives (R=R'=Me, Et, $PhCH_2$) of the bicyclic system **3** and to study their chemistry relative to the *N*-aryl derivatives

- expand the synthesis to the preparation of new bicyclic models, e.g. the thio analogue of **3**, system **N** as well as any possible analogous compounds:



N

Figure 1.9 Thio analogue of **3**.

- further explore the chemistry of **3** and of any new system of that class with particular interest in the reactivity of the P-N bond towards alcoholysis

- perform a detailed structural analysis on these compounds by X-ray diffraction in order to directly compare the different bicyclic models.

- study wherever possible, the NMR spectroscopic and GC-MS characteristics of those systems

- perform Molecular Mechanical calculations which are anticipated to contribute to better understanding of the properties and the behavior of these new heterocyclic compounds.

1.3 References

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